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PRIMARY ANASTOMOSIS IN CARCINOMA OF THE COLON*

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THE changes in the surgical management of malignant lesions of the colon effected in the last few years have resulted in a marked reduction in the mortality following radical operations on the large bowel. It was our intention to study recent colon cases with particular emphasis on the part that chemotherapy had played in improving the results. It became increasingly apparent, however, that many factors other than chemotherapy were responsible for the progress made.

With the advent of chemotherapy and its application to various fields of surgery, the value of careful preoperative preparation, of meticulous surgical technic and of individualized postoperative care has faded in the light of general enthusiasm for the new drugs now at one's command. Increasing experience, however, is demonstrating that in the conditions in which operative measures are indicated the general surgical management of the patient is still of the greatest importance and that chemotherapeutic measures are only one part — and perhaps a relatively small part — of this management.

The present study covered 65 patients with cancer of the colon, including the rectosigmoid, operated on by one of us (H. M. C.) and Dr. Thomas J. Anglem from January 1, 1943, to April 1, 1945. Although this series is not a large one it has been of value in reviewing the results obtained with the new surgical approach of recent years.

No long discussion of our general preoperative measures is needed. It is believed, however, that increasing attention to the severe anemia that many patients have and its treatment by repeated transfusions, the study and management of their protein deficiencies and the generous use of blood transfusions before, during and after operation have contributed greatly to the results attained. In addition to blood, one of the intravenous amino acid preparations has been employed, both preoperatively and postoperatively.

The methods we have used for the preparation of the colon in unobstructed cases have changed materially — and for the better. Drastic purgatives for two or three days before operation have been replaced with one or two cleansing enemas on the day of entrance, following which the colon is left alone. Most of the recent patients have been given sulfasuxidine in 2-gm. doses five times a day for three or four days before operation. There have been no toxic reactions from this drug. During this period the patient is given a high-calorie diet rich in proteins and carbohydrates and with slight residue. Clinical observations and the opinions of head nurses make it clear that the sulfasuxidine acts as a mild laxative as well as a means for reducing in some degree the bacterial flora of the gastrointestinal tract. Certainly the stools become mushy and soft and have little odor. Abdominal distention is decreased, especially in patients already partially obstructed. Regardless of the possible value of sulfasuxidine as a bactericide, it has proved to be a valuable agent simply for the preparation of the colon for surgery. It is logical, however, to believe that a drug that experimentally and clinically reduces the number of bacteria in the colon and has a very low rate of systemic reaction should be valuable in colonic surgery. That sulfasuxidine, however, is not the only factor in improving results is shown by the excellent results in these cases, in most of which the drug was not used.

Coller and Vaughan[1] have recently published their remarkable results in surgery of the colon, which was carried on largely without the use of sulfonamide drugs. Pemberton,[2] of the Mayo Clinic, on the other hand, reports equally good results in a large series of cases and believes that much of the improvement was directly related to the use of sulfonamides. The inference is clear that it is not a single factor that makes for better surgery in cancer of the colon but better general surgical management in all its details.

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In our preoperative treatment, constant Wangensteen suction drainage of the stomach was used in almost every case, a practice recently recommended by Singleton et al.[3] This was usually started the night before operation, and was always continued postoperatively until peristalsis had been re-established and the patient was passing gas by rectum. This maneuver has been of marked value in reducing postoperative complications and distress.[3]

All surgeons are strongly interested in the surgical technic best adapted for the removal of cancers of the colon. It is at once apparent from a study of our results and of the reports from most other clinics that there is no one plan of operation that is applicable to every lesion of the colon. This is true, first, because of the difference between the contents of the right colon and that of the left; second, because of the degree of obstruction and distention that usually accompanies the lesions; and finally, because of the varying degrees of operability. Relatively few surgeons now believe that all cancers of the colon, wherever situated and however complicated, are best handled by the same fundamental operative technic.

The *ideal* procedure appears to be wide removal of the tumor and its lymph node-bearing mesentery and immediate restoration of intestinal continuity. For this reason we have wherever possible refrained from resections of the Mikulicz or obstructive types and have instead used intestinal anastomoses, in either one or two stages. As the statistics show, this change has not increased the mortality rate. These figures do not, however, emphasize the gain in the patient's comfort and the decrease in trying procedures such as the repeated applications of clamps to Mikulicz spurs and the toilet of the colostomies — especially the ileocolic type — that accompany direct intestinal suture.

It seems evident, however, that there is a place for the Mikulicz type of operation, even though increasing experience indicates that it will be used less and less in the future. In the last two years we have used it primarily in the poor-risk cases with partial obstruction and some degree of infection, because it can be carried out quickly along with simultaneous decompression of the proximal bowel. The review of this series, however, strikingly demonstrates the relatively infrequent use of preliminary cecostomy in many of these patients. We believe that more frequent cecostomies will increase the opportunities to do direct intestinal anastomoses with safety and to reduce further the necessity of doing a Mikulicz operation in such cases.

* * *

In tabulating results the form used by Coller and Vaughan[1] has been followed, not only because it is extremely simple but also because it makes their relatively large series of cases comparable with ours. The sites of the tumors are listed in Table 1.

TABLE 1. *Site of Carcinoma of the Colon.*

SITE	No. of CASES
Right colon (cecum, ascending colon and hepatic flexure)	10
Transverse colon	6
Splenic flexure	6
Descending colon	6
Sigmoid	26
Rectosigmoid	11
Total	65

Ten patients had carcinoma of the right colon (Table 2). One of these was found on exploration

TABLE 2. *Treatment of Carcinoma of the Right Colon.*

TREATMENT	No. of CASES	No. of DEATHS	MORTALITY %
Palliative operation:			
Celiotomy	1	0	0
Totals	1	0	
Average			0
Resection:			
One-stage colectomy	1	0	0
Enterostomy			
Two-stage colectomy	7	1	14
Ileotransverse colostomy			
Mikulicz operation	1	0	0
Closure of colostomy			
Totals	9	1	
Average			11

to be inoperable. In the 9 other cases, the lesion was resectable. In 1 case this was safely done by a one-stage removal of the terminal ileum, cecum and ascending colon and part of the transverse colon. In 7 patients, the colectomy was done in two stages—first an ileocolostomy and later a resection of the right colon. One of these patients died of shock forty-eight hours after the second-stage operation, as a result of faulty surgical judgment in attempting it. This patient was sixty-six years of age and was short and fat, with a large diaphragmatic hernia and a seriously damaged heart. Better judgment would have classed the case as inoperable because

TABLE 3. *Treatment of Carcinoma of the Transverse Colon.*

TREATMENT	No. of CASES	No. of DEATHS	MORTALITY %
Palliative operation:			
Cecostomy with peritoneal drainage	1	0	0
Totals	1	0	
Average			0
Resection:			
End-to-end anastomosis	2	0	0
Mikulicz operation	3	0	0
Colostomy closure	3		
Second colostomy closure	1		
Small-bowel obstruction	1		
Totals	5	0	
Average			0

of the patient's general condition. The patient receiving the Mikulicz procedure was a young man with a large, infected, partly obstructing tumor in the hepatic flexure. It is probable that today the procedure adopted would be decompression with a Miller–Abbott tube and a two-stage intestinal anastomosis and right-sided colectomy.

There were 6 cases of cancer of the transverse colon (Table 3). One was inoperable and only a cecostomy was done. In 5, the lesion was resectable. In 2 cases a primary resection and end-to-end suture without cecostomy were done, and in 3 a Mikulicz-type resection and later colostomy closure. In one of these 3 cases, a secondary closure of the colostomy became necessary after several weeks in the hospital. In another, reoperation for small-bowel obstruction was required — a total of eight operations and many applications of clamps to the colostomy spur in 3 cases. In the third case, the Mikulicz procedure was life-saving, the patient having had a resection of the right colon for cancer twelve years previously, but in the other two cases it is certain that a preliminary cecostomy could have been safely followed by an end-to-end suture. This, in the light of recent experience, would have been safer and better than the procedure adopted.

There were 6 cases of cancer of the splenic flexure (Table 4). A palliative operation was done in 3 of

TABLE 4. *Treatment of Carcinoma of Splenic Flexure.*

TREATMENT	No. of CASES	No. of DEATHS	MORTALITY %
Palliative operation:			
End-to-end suture colon; resection of spleen and part of stomach	1	0	0
Mikulicz resection of splenic flexure and part of ileum	1	1	100
Colo-colostomy	1	0	0
Totals	3	1	
Average			33
Resection:			
End-to-end anastomosis	2	0	0
Resection of part of pancreas	1		
Mikulicz operation	1	0	0
Colostomy closure	1		
Totals	3	0	
Average			0

these, in 2 of which it was an extensive and radical procedure. One of these patients died after a Mikulicz resection of the splenic colon and a resection of part of the ileum and a side-to-side anastomosis. It is to be noted, however, that in 1 case the colon was resected with an end-to-end anastomosis and that the spleen, along with part of the stomach, was also removed, with immediate normal recovery. In 2 of the remaining cases, the cancers

TABLE 5. *Treatment of Carcinoma of the Descending Colon.*

TREATMENT	No. of CASES	No. of DEATHS	MORTALITY %
Resection:			
End-to-end anastomosis	4	0	0
Resection of small bowel	1	0	0
Mikulicz operation	2	0	0
Preliminary cecostomy	3	0	0
Colostomy closure	0		
Totals	6	0	
Average			0

of the splenic flexure were resected and an end-to-end suture was carried out without difficulty. In the last case, a Mikulicz operation was done and the colostomy was later closed.

There were 6 cases of cancer of the descending colon — all resectable (Table 5). In 4 cases a resection and end-to-end suture were done, with no deaths. In 1 of these a piece of small bowel was also removed. In 2 cases, a Mikulicz resection was done. No attempt was made to close the colostomy of one of these patients because of age and disabilities; the second patient was a recent resection. We believe that today we could safely handle each case with a one-stage resection following preliminary cecostomy with a catheter.

Twenty-six patients had lesions in the sigmoid (Table 6). Seven cases were inoperable. Three of

TABLE 6. *Treatment of Carcinoma of the Sigmoid.*

TREATMENT	No. of CASES	No. of DEATHS	MORTALITY %
Palliative operation:			
Cecostomy	3	2	67
Colostomy	4	0	0
Totals	7	2	
Average			29
Resection:			
End-to-end anastomosis	8	0	0
Preliminary cecostomy	3		
Mikulicz operation	11	2*	18
Preliminary cecostomy	1		
Colostomy closure	5		
Totals	19	2	
Average			11

*One of these patients died following closure of the colostomy, apparently from coronary thrombosis.

these had a cecostomy only, and 2 of them died within hours or days of this procedure. In 4 cases, exploration and permanent colostomy was done, with no deaths. In the other 19 cases resection was done. In 8 of these, the operation was an end-to-end suture, with no deaths. Three of these patients had a preliminary cecostomy. It would probably have been safer to have done a preliminary cecostomy or at least a complementary one in all, although none of the patients without cecostomy caused any concern. This is the type of case in which Wangensteen suction seems especially valuable. The remaining 11 patients received Mikulicz resections, and 1 of these had a preliminary cecostomy. One patient died suddenly from a pulmonary embolus after the first-stage operation, having been up and about for five days. Five of these 11 patients have had their colostomies closed, and 1 of these 5 died after the second operation, apparently from a coronary thrombosis. Many Mikulicz resections of the sigmoid were done on feeble, elderly people or patients with liver metastases in whom it was not planned to close the colostomy. We now believe that it would render such patients a better service to do the resection in one stage, with an end-to-end suture and complementary cecostomy. With widening experience we shall probably be forced into fewer and fewer Mikulicz operations for removing cancers of the sigmoid.

Eleven patients had cancer of the rectosigmoid (Table 7). Five of these were inoperable, but in 6 it was possible to resect the lesion, with no deaths.

In 2 cases, resection and end-to-end suture were done. In an elderly man the rectosigmoid was opened and sutured following the removal of a malignant polyp. In 2 cases, an abdominoperineal resection of the lower sigmoid and rectum was done. In an extremely obese woman a preliminary colostomy and posterior resection of the rectum were performed. Anatomically the rectosigmoid is a fairly precise area, but at the operating table whether the site of the lesion is called "lower sigmoid," "rectosigmoid," or "high rectum." is often a matter of the surgeon's opinion. It may be that some cases classified as cancer of the rectosigmoid were in reality cancer of the sigmoid or even the rectum. In the 5 inoperable cases, only a colostomy could be done because of the extent of the growth. One of these patients died the day after operation, apparently from a pulmonary embolus. In 1 case, a preliminary cecostomy was done because of obstruction.

TABLE 7. *Treatment of Carcinoma of the Rectosigmoid.*

TREATMENT	No. OF CASES	No. OF DEATHS	MORTALITY %
Palliative operation:			
Colostomy	5	1	20
Preliminary cecostomy	1		
Totals	5	1	
Average			20
Resection:			
End-to-end anastomosis	2	0	0
Colotomy and excision of polyp	1	0	0
Abdominoperineal operation (one-stage excision)	2	0	0
Preliminary cecostomy	1		
Posterior resection	1	0	0
Preliminary colostomy	1		
Totals	6	0	
Average			0

* * *

The over-all mortality for the entire series of 65 cases was 12 per cent, 8 patients dying in the hospital (Table 8). In 17 cases, the lesion was inoperable and only palliative procedures were done. Five of these patients died, a mortality of 29 per cent. In 48 cases, the lesion was operable. Three of these patients died, a mortality of 6 per cent.

In all intestinal sutures some type of so-called "aseptic anastomosis" was used. Today, when there are so many methods and instruments for such a procedure, there seems relatively little excuse for employing an open anastomosis. Even if it were believed that the bowel contents could be sterilized by chemotherapy, we should still use some type of aseptic anastomosis. Our preference is naturally for the use of the Furniss clamp or our modification of it.

For sutures we use multiple, short, running sutures of nylon or silk, taking great pains to be sure that the blood supply is adequate at the ends of the bowel, and being careful not to disturb the blood supply when sewing up the mesentery.

We stopped clearing away fat tabs and epiploic appendages from the area of the suture line some years ago, and now sew completely through them or use them to turn over onto the suture line.

SUMMARY AND CONCLUSIONS

In this series of 48 cases of resectable cancer of the colon, intestinal anastomoses were done in 34—in 27 as primary operations and in 7 as secondary (right colon) procedures. One patient in this group died of shock after a second-stage right colectomy, a mortality of 3 per cent. Mikulicz resection was done in 18 cases, with colostomy closure in 10. In 8 cases, the colostomies were not closed. Two patients died, — one of embolism and the other of thrombosis, — a mortality of 11 per cent.

We believe that the Mikulicz operation in cancer of the colon should be used only in cases in which it seems impossible to re-establish continuity of the intestine by direct intestinal anastomosis, or unwise to attempt it.

With careful preoperative preparation, including preliminary cecostomies as indicated, with meticu-

TABLE 8. *Mortality Statistics in All Cases.*

TYPE AND SITE OF OPERATION	No. OF CASES	No. OF DEATHS	MORTALITY %	CAUSE OF DEATH
Palliative operation:				
Right colon	1	0	0	
Transverse colon	1	1	100	Obstruction and peritonitis
Splenic flexure	3	1	33	Peritonitis from leakage
Descending colon	0	0	0	
Sigmoid	7	2	29	Obstruction and peritonitis; pulmonary embolism.
Rectosigmoid	5	1	20	
Totals	17	5		
Average			29	
Resection:				
Right colon	9	1	11	Shock (bad judgment)
Transverse colon	5	0	0	
Splenic flexure	3	0	0	
Descending colon	6	0	0	
Sigmoid	19	2	11	Coronary thrombosis; pulmonary embolism.
Rectosigmoid	6	0	0	
Totals	48	3		
Average			6	
Grand totals	65	8		
Grand average			12	

lous surgical technic and with individualized postoperative treatment, most patients having cancer of the colon can be safely operated on by resection of the lesion and intestinal anastomosis, and this is the method of choice.

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THIOURACIL AS A CAUSE OF NEUTROPENIA AND AGRANULOCYTOSIS*

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THIOURACIL is an effective agent in the treatment of toxic goiter,[1-3] but this effectiveness is frequently associated with toxic reactions of varying degrees of seriousness. The most important of these manifestations that have been reported are swelling of the submaxillary salivary gland, drug fever, dermatitis, jaundice, and neutropenia and agranulocytosis.[4, 5] Although most of these complications are formidable, none except agranulocytosis have produced fatalities. The purpose of this study is to inquire further into the undesirable effects of thiouracil on the blood.

Sixty-two patients, all but 1 of whom had thyrotoxicosis, have been treated with thiouracil for varying periods of time. Four patients developed neutropenia or agranulocytosis, and in 1 of the cases death ensued. These cases will be described in detail because of the insight they give into the mechanism of the deleterious effect of thiouracil on hemopoiesis, especially with regard to the granulocytes.

CASE 1. F. M., a 56-year old housewife, was admitted to the hospital on March 31, 1943, because of fatigue and nervousness of 7 months' duration and dyspnea, palpitation, tremors and weight loss in the preceding 3 months.

Physical examination revealed a hyperactive patient with staring eyes and flushed facies. The skin was moist and warm. There were fine tremors of the extended tongue and hands. The thyroid gland was diffusely enlarged to about twice its normal size. The blood pressure was 110/70. The basal metabolic rate on admission was + 30 per cent. All other pertinent laboratory data were normal.

The patient was given 0.6 gm. of thiouracil for 17 days, 0.5 gm. for 6 days and 0.2 gm. daily thereafter. The basal metabolic rate gradually fell to −2 per cent, and she was able to leave the hospital 26 days after entry.

The patient was thereafter observed at weekly intervals in the Endocrine Clinic, where the white-cell count, basal metabolic rate, weight and pertinent clinical features were noted. The giving of 0.2 gm. of thiouracil daily was continued. Thirty days after the beginning of treatment, the basal metabolic rate was −9 per cent. By the end of 8 weeks, it had dropped to −19 per cent and puffiness of the eyelids had appeared. After 10 weeks, the basal metabolic rate was −19 per cent, the blood cholesterol was 328 mg. per 100 cc., and there was increasing puffiness of the eyelids and face. After 12 weeks, the patient complained of irritability and sluggishness and showed marked facial puffiness, with a thick, dry skin. The basal metabolic rate was −24 per cent, and the blood cholesterol 367 mg. per 100 cc. Thiouracil was stopped because of myxedema. The white-cell count throughout the first 3 months of treatment ranged between 6400 and 10,500, with abundant granulocytes always present.

Thiouracil was not administered for the next 4½ months. In this period, the basal metabolic rate rose to + 9 per cent and mild symptoms of thyrotoxicosis gradually redeveloped. Thiouracil was resumed on October 15 in a dosage of 0.2 gm. daily. After 2 weeks, the basal metabolic rate had dropped to −4 per cent and the thyrotoxic symptoms had disappeared, and after 4 weeks, it was −13 per cent. By the 11th week, the patient looked slightly myxedemic and had a basal metabolic rate of −19 per cent and a blood cholesterol of 312 mg. per 100 cc. The dosage of thiouracil was accordingly reduced to 0.1 gm. daily. After 20 days, the thiouracil was again stopped because of progressive signs and symptoms of myxedema. Three weeks later, the basal metabolic rate had risen to + 3 per cent and the patient felt and looked well. When she had not taken thiouracil for 7 weeks, however, mild thyrotoxic symptoms again appeared, associated with a rise in the basal metabolic rate to + 21 per cent.

A third course of thiouracil, 0.2 gm. daily, was therefore begun on March 16, 1944, approximately 1 year after the initiation of treatment. On April 15, the basal metabolic rate was + 13 per cent, and as the patient still showed mild signs and symptoms of thyrotoxicosis, the thiouracil was continued. The white-cell count at that time was 6500.

On the following day, the patient was fitted with new dentures and noted tenderness in the roof of the mouth. On April 17, a sore throat developed, followed by a chill and a rise in temperature to 103.5°F. Examination showed an acutely ill woman with flushed facies, coated tongue, large, reddened tonsils covered with a grayish exudate and tender, swollen lymph glands at the angles of the jaw. The white-cell count was 1000, with no granulocytes. Thiouracil was stopped and the patient was admitted to the hospital.

Treatment consisted of three blood transfusions, 5 gm. of sodium sulfadiazine and 9 gm. of sodium sulfamerazine intravenously, 270 cc. of Pentnucleotide intramuscularly, liver extract and 150,000 units of penicillin. Ulcerations developed in the throat and tonsils. The white-cell count ranged between 900 and 1650. The hemoglobin was 11.3 to 12.5 gm. per 100 cc., and the red-cell count averaged 4,000,000. No polymorphonuclear cells appeared at any time, but on the day before death 1 myelocyte was seen in a count of 25 cells. Two sternal bone-marrow biopsies were done on the 2nd and 4th hospital days; both showed a hypoplastic marrow with granulocytic aplasia.§ The patient died suddenly on the 6th day.

Autopsy showed that the immediate cause of death was tracheal obstruction, caused by a gelatinous mucoid plug that started just below the vocal cords and extended deep into the bronchi, with almost complete occlusion. This obstruction produced widespread pulmonary atelectasis and congestion which in turn gave rise to marked dilation of the right side of the heart. The pharyngeal ulcers that had been noted clinically were filled with necrotic plugs containing large numbers of bacilli and cocci, without cellular reaction to the necrotic tissue. The thyroid gland was enlarged to about twice its normal size and contained a 6-mm. nodule. Microscopically there was alveolar hyperplasia. The marrow in the femur was yellow and fatty, with only a few small islands

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§The bone-marrow studies in this case were carried out by Dr. Benjamin Alexander of the Hematology Clinic and Laboratory.

of marrow cells. In the vertebras, sternum and ribs the marrow was abundant, pasty and slightly brownish. Sections from the ribs were at least half fat; the remainder consisted of marrow-forming cells, composed of an equal mixture of large, undifferentiated cells with a bluish cytoplasm and of normoblasts. No eosinophilic myelocytes were present.

Summary. This patient with toxic goiter received three courses of thiouracil during a period of 1 year. The first course of thiouracil with an average daily dose of 0.2 gm. lasted 3 months and was followed by myxedema and a remission of 4½ months' duration. The second course, also with an average daily dose of 0.2 gm., lasted for 14 weeks and was followed by the reappearance of myxedema and a remission lasting for 7 weeks. In the third and final course, the patient received a daily dose of 0.2 gm. of thiouracil for 4 weeks, at the end of which agranulocytosis suddenly appeared, followed by death in 6 days. Post-mortem examination showed extensive granulocytic hypoplasia of the marrow, ulcerative pharyngitis, an occluding tracheobronchial mucus plug, pulmonary congestion and atelectasis and acute dilatation of the right auricle and ventricle. The thyroid gland showed alveolar hyperplasia and hydropic degeneration, with the absence of colloid and of lymphocytic infiltration.

CASE 2. H. S., a 57-year old upholsterer, entered the hospital on September 3, 1942, because of severe angina pectoris and heart failure. He had been admitted 4 months previously for congestive heart failure.

Examination showed dyspnea, orthopnea and cyanosis and engorged neck veins. The heart was enlarged downward and to the left and had a loud systolic murmur at the mitral area. Both lung bases showed numerous moist rales. The liver was enlarged to 4 fingerbreadths below the right costal margin. Ascites and moderate ankle edema were present. The blood pressure was 140/110. Urinalyses showed specific gravities ranging between 1.010 and 1.020, a ++++ test for albumin, no sugar and varying numbers of red and white cells, with occasional hyaline and granular casts in the sediment. The blood nonprotein nitrogen varied between 45 and 64 mg. per 100 cc. The blood carbon dioxide combining power was 46 vol. per cent. Numerous electrocardiograms showed a normal rhythm, with defective intraventricular conduction, left-axis deviation and prominent Q waves in Leads 1, 2 and 3. The hemoglobin was 110 per cent (16.0 gm.), the red-cell count was 5,600,000, and the white-cell count was 7900, with 64 per cent neutrophils, 34 per cent lymphocytes and 2 per cent monocytes. Roentgenography showed a hypertensive heart with marked pulmonary congestion.

The patient was treated with bed rest, salt restriction, digitalis, mercurial diuretics and nitroglycerin, but this regime failed to benefit the angina pectoris or establish cardiac compensation. Total thyroidectomy was considered, but was not undertaken because of impaired renal function. An attempt to produce myxedema by the use of thiouracil was therefore substituted. The basal metabolic rate in a series of five determinations ranged between +9 and +19 per cent. This elevation was attributed to heart failure, since the blood velocity (arm to tongue) was prolonged to 35 seconds and the venous pressure increased to 15 cm. of water.

On September 25, 1942, thiouracil was begun in doses of 0.8 gm. daily. At that time the red-cell count was 5,150,000, the hemoglobin 112 per cent (16.2 gm.), and the white-cell count 8000, with 75 per cent neutrophils, 23 per cent lymphocytes and 2 per cent monocytes. After 7 days the dosage of thiouracil was reduced to 0.6 gm. At that time, the hemoglobin was 114 per cent (16.5 gm.), the red-cell count was 5,900,000, and the white-cell count was 9300, with 61 per cent neutrophils, 31 per cent lymphocytes, 3 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils. After 18 days, the thiouracil dosage was reduced to 0.4 gm. daily because on the preceding day the leukocytes had numbered 3300, with only 32 per cent neutrophils. The hemoglobin was 104 per cent (15.1 gm.) and the red-cell count 5,250,000.

Leukopenia continued despite the reduction of dosage, and 3 days later the white-cell count was 2100, with 7 per cent neutrophils; the hemoglobin had fallen to 90 per cent (13.1 gm.) and the red-cell count to 4,000,000. Thiouracil was stopped, and the patient was transfused with 750 cc. of whole blood and given 40 cc. of Pentnucleotide daily. On the following day, the white-cell count was 3300, with 11 per cent neutrophils. Thereafter the granulocytes increased steadily in percentage and in total numbers, so that by the end of 6 days the white-cell count was 6700, with 64 per cent neutrophils (Table 1). During the period of neutropenia, the patient had a single rise in temperature to 101.4°F. and developed an urticarial dermatitis. The basal metabolic rate was not decreased as a result of the administration of thiouracil.

TABLE 1. *Hematologic Findings in Case 2.*

DATE	WHITE-CELL COUNT	GRANULOCYTE COUNT	DIFFERENTIAL COUNT N	L	M	E	B	HEMOGLOBIN*	RED-CELL COUNT	REMARKS
			%	%	%	%	%	%		
1942									*x10⁶*	
9–20	7,900	5,050	64	34	2	0	0	110	5.6	
9–26	8,000	6,000	75	23	2	0	0	112	5.2	Thiouracil, 0.8 gm. daily, begun 9–25
10–1	9,300	5,675	61	31	3	4	1	114	5.9	Thiouracil reduced to 0.6 gm. daily
10–19	3,300	1,060	32	50	17	0	1	104	5.3	Thiouracil reduced to 0.4 gm. daily
10–20								106	5.3	Urticarial dermatitis; thiouracil omitted.
10–21	2,100	147	7	72	21	0	0	92	4.0	500 cc. whole blood; 40 cc. Pentnucleotide.
10–22	3,300	363	11	68	20	0	0			250 cc. whole blood; 40 cc. Pentnucleotide.
10–23	3,800	1,370	36	54	10	0	0			
10–24	5,300	3,180	60	35	5	0	0			
10–25	3,700	1,590	43	46	10	0	1	90	4.7	
10–26	6,700	4,290	64	29	7	0	0			
10–27	8,300	5,320	64	29	6	0	1			

*In this and subsequent tables 100 per cent hemoglobin is considered to be equivalent to 14.5 gm. per 100 cc.

The patient was discharged on October 31, but was readmitted on February 10, 1943, because of recurrence of heart failure and died on April 29.

Autopsy showed aneurysm of the left ventricle, coronary sclerosis, left-ventricular hypertrophy, bronchopneumonia, bronchiectasis, a bronchiectatic cavity with small lung abscesses, chronic glomerulonephritis and chronic passive congestion. The thyroid gland was normal on gross and microscopic examination. The bone marrow was also normal, with active formation of both red and white blood cells.

Comment. In this patient with chronic heart failure and angina pectoris, the production of myxedema was attempted through the administration of thiouracil — 0.8 gm. daily for 6 days, 0.6 gm. daily for 18 days and 0.4 gm. daily for 2 days. On the 25th day leukopenia and neutropenia were noted, and on the 27th day there was severe neutropenia, associated with a slight reduction in the hemoglobin level and the red-cell count. Simultaneously with the onset of the neutropenia, an urticarial dermatitis appeared. Complete temporary recovery ensued following stoppage of the drug and treatment with transfusions and Pentnucleotide.

CASE 3. L. C., a 34-year-old, unmarried woman, an office worker, entered the hospital on July 19, 1944, because of tremors of the hands, irritability, palpitation, increasing appetite and a weight loss of 15 pounds during the preceding 3 weeks. Staringness of the eyes, excessive perspiration, fatigability and swelling of the neck had also been observed. For 6 months, menstruation had been scanty but regular. A brother had undergone thyroidectomy for toxic goiter.

Physical examination disclosed a thin, overactive, apprehensive and trembling young woman with stary eyes. The skin was moist, flushed and warm. The thyroid gland was diffusely enlarged to twice its normal size. The heart showed a moderate systolic murmur, maximal at the pulmonic area and extensively transmitted over the precordium. The heart rate was 120, the rhythm was regular, and the blood pressure was 124/76. There was a fine tremor in the hands and legs. Urinalysis showed no abnormalities. The hemoglobin was 76 per cent (11.0 gm.), the red-cell count 3,720,000, and the white-cell count 11,100, with 68 per cent neutrophils, 27 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. The blood cholesterol was 145 mg. per 100 cc., and the icterus index 6. The basal metabolic rate on July 19 was +35 per cent and on July 20 was +27 per cent.

Thiouracil, 1.0 gm. daily, was begun on July 21. Daily white-cell and differential counts were made. As shown in

Table 2, the patient exhibited the usual lymphocytosis characteristic of hyperthyroidism. She tolerated the drug well until July 28, when a rise in temperature to 99.5°F. occurred. Thiouracil was continued in the same dosage. On the next day, the temperature rose to 100.5° F. and the patient complained of a sore throat. Examination showed injection of the posterior pharyngeal wall and a white-cell count of 4800, contrasted with one of 10,600 on the previous day. The percentage of neutrophils had not changed. On July 30, the patient complained of sore throat and chilly sensations. Examination of the blood showed moderate leukopenia and beginning neutropenia. Thiouracil was stopped. On the next day, the temperature rose to 100°F. and the patient complained of malaise and headache. On August 1, she was afebrile and symptom-free, but the blood examination showed persistence of the neutropenia and a moderate eosinophilia. Following this there was gradual improvement in the blood picture, so that on August 4 the white-cell count and the percentage of neutrophils approached those found prior to the administration of thiouracil.

TABLE 2. *Hematologic Findings in Case 3.*

DATE	WHITE-CELL COUNT	GRANULOCYTE COUNT	DIFFERENTIAL COUNT N %	L %	M %	E %	HEMOGLOBIN %	RED-CELL COUNT x10⁶	REMARKS
1944									
7-19	11,100	7,550	68	27	5	2	76	3.7	B.M.R. + 35%
7-21	6,150	3,320	54	40	4	2			Thiouracil, 1.0 gm. daily, begun 7-21
7-22	6,250								B.M.R. + 27%
7-24	9,400	5,260	56	35	7	2			
7-25	7,800	4,300	55	40	5	0			
7-26	10,100								
7-27	10,600	6,675	63	25	9	3			
7-29	4,800	2,930	61	23	10	6			Fever up to 100.5°F.
7-30	5,100	2,450	48	40	9	3			Thiouracil omitted
	4,700								
8-1	5,000	1,700	34	49	6	11			B.M.R. + 13%
8-2	7,900	3,560	45	43	8	4			
8-3	6,100	2,930	48	37	11	4			
8-4	7,900	4,030	51	38	10	1			

The final basal metabolic rate on August 2 was +13 per cent. Administration of 10 drops daily of saturated solution of potassium iodide was begun on that day, and the patient was discharged home on August 5.

Comment. This patient with diffuse toxic goiter was treated with 1.0 gm. of thiouracil daily for 7 days, when she developed a toxic reaction manifested by sore throat, fever and granulocytopenia. Stopping of the drug was followed by prompt recovery without further treatment. The patient exhibited the lymphocytosis associated with toxic goiter and had an average neutrophil count of 5400 before the toxic reaction. Following clinical recovery from this reaction, the neutrophils remained at the comparatively low level of 3500. At the height of the toxic reaction, the count dropped to 1700. Significant eosinophilia developed during recovery.

CASE 4. E. G., a 33-year old housewife, entered the hospital on June 26, 1944, complaining of irritability and easy fatigue. There had been a weight loss of 20 pounds in the preceding 9 months, and a goiter had appeared 6 months previously. There had also been increased appetite, hyperhidrosis, palpitation and decreased tolerance to heat.

On examination the patient was restless. There was moderate exophthalmos and slight puffiness of the eyelids. The skin was flushed, warm and moist. The thyroid gland was diffusely enlarged to five times its normal size and exhibited a loud bruit and widespread thrill. There were fine tremors of the tongue and hands. The heart was not enlarged, its rhythm was regular at a rate of 134, and there were no murmurs. The blood pressure was 140/70. Urine examination revealed no abnormalities. The initial and subsequent hematologic findings are given in Table 3. The fasting blood cholesterol was 141 mg. per 100 cc., and the nonprotein nitrogen 29 mg. The icterus index was 6. The initial basal metabolic rate was +43 per cent.

The beginning treatment consisted of bed rest, a high-calorie diet and small doses of phenobarbital. Within a few days there appeared an erythematous maculopapular rash, which was interpreted as due to the phenobarbital. The drug was omitted and the rash disappeared after 4 days. On July 10, 1.0 gm. of thiouracil daily was begun. This was continued until July 20, when the dosage was reduced to 0.6 gm. daily. On July 31, it was further reduced to 0.4 gm.

TABLE 3. *Hematologic Findings in Case 4.*

DATE	WHITE-CELL COUNT	GRANULOCYTE COUNT	DIFFERENTIAL COUNT N %	L %	M %	E %	HEMOGLOBIN %	RED-CELL COUNT x10⁶	REMARKS
1944									
6-26	5,100						88	4.3	B.M.R. + 43%
7-6	7,600	3,500	46	44	10	0	90	4.9	B.M.R. + 37%
7-11	7,000								Thiouracil, 1.0 gm. daily, begun 7-10
7-12	8,100	4,550	56	39	4	1			
7-13	5,000								
7-14	6,400	4,355	68	25	6	1			
7-15	7,700								
7-17	12,000	9,500	79	14	5	2			
7-18	4,600	3,080	67	25	6	2			B.M.R. + 32%
7-19	7,100								
7-20	6,200								Thiouracil, 0.6 gm.
7-21	9,000	5,580	62	30	1	2			
7-22	6,200								
7-24	4,200	3,280	78	22	0	0			B.M.R. + 26%
7-25	5,200	3,900	75	22	2	1			
7-26	6,500								
7-27	4,800	3,650	76	17	3	4			
7-28	4,000	2,880	72	24	2	2			
7-29	4,200	2,900	69	25	2	4			B.M.R. + 14%
7-31 a.m.	3,000	1,860	62	30	5	3			Temperature 99.4°F.; sore throat; thiouracil, 0.3 gm.
p.m.	3,600								
8-1 a.m.	3,450	1,415	41	43	9	6			Temperature 100°F.; thiouracil omitted.
p.m.	4,000	1,760	44	44	10	2			
8-2 a.m.	4,600	1,840	40	50	8	1			Temperature 99°F.
p.m.	4,100	1,270	31	48	1	12			
8-3	4,700	2,780	59	32	6	3			Normal temperature
8-18	14,900	11,600	78	14	5	3			

By then, the basal metabolic rate had dropped to +14 per cent. As shown in Table 3, the patient had had leukopenia for several days. On August 1, the temperature rose to 100.5°F., there was a slight sore throat and further leukopenia and neutropenia were evident. Thiouracil was stopped, but there was no further therapy of the granulocytopenia. The blood picture gradually returned to normal. A saturated solution of potassium iodide was given for the treatment of the thyrotoxicosis. The patient was discharged on August 4 and was followed in the Endocrine Clinic.

Comment. This thyrotoxic patient received 1.0 gm. of thiouracil daily for 10 days, 0.6 gm. daily for the following 10 days and 0.4 gm. daily for the next 2 days, when the drug was stopped because of sore throat, fever and granulocytopenia. Clinical and hematologic improvement rapidly ensued. At the height of the toxic reaction, the patient looked and felt well. The neutrophil count averaged 4275 before the toxic reaction and dropped to 1270 at the height of the reaction. It is significant that the number of granulocytes dropped well below the average level 3 days before fever and sore throat appeared. As in Case 3, marked eosinophilia signalized recovery. Moreover, as can be seen in Table 3, this patient exhibited the usual lymphocytosis of hyperthyroidism. Control of the thyrotoxicosis manifested itself by a normal neutrophil-lymphocyte ratio. With the development of toxic neutropenia there was reversion to the original neutrophil-lymphocyte ratio, but with an abnormally low number of granulocytes. The latter finding and the associated clinical phenomena of pharyngitis and fever adequately established the diagnosis of thiouracil neutropenia.

CASE 5. A. M., a 32-year-old housewife, entered the hospital on November 3, 1944, with the complaints of nervousness, thermophobia, hyperhidrosis, tremor of the hands and palpitation. There had been a weight loss of 14 pounds and a scanty menstrual flow during the preceding 9 months.

Examination showed restlessness; a flushed, warm, moist skin; lustrous, staring eyes without exophthalmos or lid lag; diffuse enlargement of the thyroid gland to twice its normal size; a slight basal and apical systolic murmur, without heart enlargement; a blood pressure of 140/70; and fine rapid tremors of the hands. Urinalysis showed no abnormalities. Detailed hematologic observations were made and are pre-

sented in Table 4. The fasting blood sugar was 83 mg. per 100 cc. and the cholesterol 162 mg. The icterus index was 6. The basal metabolic rate before treatment varied between +19 and +29 per cent.

Thiouracil in daily doses of 1.0 gm. was begun on November 9, and was continued at that level until November 12, when the dosage was reduced to 0.8 gm. This amount was administered until November 26, when the patient was discharged. Thereafter, she took 10 drops of saturated solution potassium iodide daily. The response to thiouracil was prompt. At the end of 4 days of its administration, the basal metabolic rate had dropped to +6 per cent and there was marked clinical improvement. By the 10th day, it had dropped to −6 per cent, and it remained at that level until discharge. This remission has been further maintained by iodide medication.

TABLE 4. *Hematologic Findings in Case 5.*

DATE	WHITE-CELL COUNT	GRANULOCYTE COUNT	DIFFERENTIAL COUNT N %	L %	M %	E %	HEMOGLOBIN %	RED-CELL COUNT $\times 10^6$	REMARKS
1944									
11-3	6,000	4,560	76	16	8		90	4.9	B.M.R. +29%
11-10	6,000	3,660	61	25	10	4	94	5.5	B.M.R. +17% on 2nd day of thiouracil, 1.0 gm. daily
11-11	4,950	3,620	73	18	8				
11-12	6,400	4,550	71	21	6	2			Thiouracil reduced to 0.8 gm. daily
11-14	5,650	4,180	74	19	3	4			B.M.R. +6%
11-15	5,100	3,820	75	17	4	4		3.9	
11-16 a.m.	4,000	2,320	58	32	2	7	84		B.M.R. +1%
p.m.	5,100								
11-17 a.m.	4,100	3,080	75	20	2	3			
p.m.	4,400						84	4.5	
11-18	4,500	3,600	80	15	2	3			B.M.R. −3%
11-19	3,950	2,840	72	18	7	3			
11-20	4,700	3,380	72	22	5	1			
11-21	5,500	3,850	70	22	3	5			
11-22	6,100	4,950	81	12	2	5			B.M.R. −6%
11-23	6,350	4,700	79	16	2	3			
11-24	4,900	3,820	78	18	1	3			
11-25	5,700	4,275	75	20	2	3			B.M.R. −6%
11-26	6,400								Thiouracil omitted
12-8	7,100	5,850	83	15	1	1	77	4.1	

Comment. This case is included to illustrate a benign hematologic reaction to the administration of thiouracil, characterized by slight leukopenia and neutropenia, with complete recovery in spite of continued administration of thiouracil.

DISCUSSION

In early animal investigations of the sulfur-containing compounds that simultaneously produce thyroid hyperplasia and inhibit hormone production, no reference is made to effects on hemopoiesis.[6–8] When thiouracil and thiourea were utilized in the treatment of patients with toxic goiter, neutropenia and agranulocytosis appeared among the first toxic manifestations.[1–3] This effect was at first ascribed to overdosage or idiosyncrasy, but subsequent experience indicates that the etiologic mechanism of the hemopoietic depression is far from clear.

Astwood[4] has reported 1 case of agranulocytosis and 1 case of marked leukopenia among 62 cases treated with thiouracil. The agranulocytosis in the first case was ascribed to the excessive dose of 2.0 gm. daily. In the second case, which resembled Case 2, a patient with heart disease without thyrotoxicosis received 0.6 gm. of thiouracil for sixty-two days and 0.3 gm. for thirty-one days. On the eighty-fifth day, sulfamerazine was given for a streptococcal infection of the finger, and by the ninetieth day the granulocyte count had dropped to 100, with a white-cell count of 2000. Coincidentally, ulcerative stomatitis and pharyngitis developed. Recovery occurred after ten days. Despite the use of sulfamerazine, thiouracil seems implicated as the probable etiologic agent in this case because of the rarity of neutropenia during the first week of sulfonamide therapy. Although at first emphasizing the dosage factor in the causation of thiouracil neutropenia, Astwood has more recently raised the question of hypersensitivity tending to occur in allergic subjects.

Williams and Clute,[3] in reviewing their experience with 72 cases of thyrotoxicosis treated with thiouracil, report 1 case of agranulocytosis and 1 case of neutropenia. In the latter case, the granulocyte count was 640 and the white-cell count 3200. Administration of thiouracil was continued, and the numbers of granulocytes and white cells returned to normal. These authors noted other mild leukopenic reactions, which they explained as part of the thyrotoxic syndrome, unrelated to the administration of thiouracil. In subsequent metabolic studies, Williams and his co-workers[9] found the human bone marrow to be one of the tissues most highly saturated with the drug. They also found the concentration of thiouracil in white cells to be greater than that in red cells.

Gabrilove and Kert[10] observed 1 case of neutropenia in 9 patients treated with thiouracil. The granulocyte count dropped from an initial level of 3420 to 1520 after 1 gm. of thiouracil had been given for sixteen days, when the drug was stopped.

Paschkis and his co-workers[11] used thiouracil in the treatment of 17 cases of thyrotoxicosis and observed 1 case of leukopenia, with a white-cell count of 2500, after eight months of treatment with 1.0 gm. of thiouracil daily. The count returned to normal within three days after stoppage of the drug, and was again depressed within forty-eight hours after resumption of treatment.

Sprunt[12] treated 22 thyrotoxic patients with thiouracil in dosages up to 0.8 gm. daily. Nine patients developed significant leukopenia, especially involving the granulocytes, with white-cell counts as low as 3000. The white-cell count regularly increased with cessation of therapy. When the drug was readministered in smaller doses, recurrence of neutropenia was infrequent.

In 1944, McGavack et al.[13] published a review of all toxic reactions to thiouracil that had been reported to that time and added their own experience with its use in 26 thyrotoxic patients. Three of these patients developed leukopenia, with intensification of the lymphocytosis already present. The respective white-cell counts were 3500, with 1400 neutrophils; 4500, with 1400 neutrophils; and 2500, with 1200 neutrophils. These neutropenic

reactions occurred between one week and five months following the daily administration of 0.3 to 0.4 gm. of thiouracil. The drug was continued, with return of the hemogram to normal. No associated clinical symptoms of toxicity were mentioned. Two additional cases were reported by these authors, one with agranulocytosis and the other with neutropenia and both with clinical manifestations of toxicity. In the first case, agranulocytosis occurred in the sixth week of treatment at a thiouracil dosage level of 0.5 gm. daily. Gingivitis, pharyngitis and fever were the chief clinical manifestations. On the forty-second day, the white-cell count was 3500, with no granulocytes. Stoppage of the drug and whole-blood transfusions were the only methods of treatment. After five days granulocytes appeared in the blood stream, and after thirteen days recovery was complete. Bone-marrow study revealed a decrease in the myeloid series and an increase in the lymphocytes, hematogones and reticulum cells. The authors ascribed this toxic reaction to the continued large dose of the drug (0.5 gm. daily). The second case developed fever, urticaria and leukopenia after taking 0.5 gm. daily of thiouracil for six days. Omission of the drug was followed by recovery over a ten-day period. Readministration of a single dose of the drug resulted in reappearance of all the toxic symptoms. During the initial toxic reaction, the white-cell count dropped from 12,200, with 10,120 neutrophils, to 9100, with 3640 neutrophils, at the height of the reaction.

Himsworth,[14] in a discussion of the treatment of thyrotoxicosis with thiouracil, reports 1 fatal case of agranulocytosis in a series of 22 cases. The incidence of neutropenia in these cases is not mentioned.

A case of severe neutropenia following the administration of thiouracil for toxic goiter was reported by Meyer.[15] Initially the patient received 0.6 gm. daily for six weeks. Remission was incomplete, so that the dosage was increased to 1.2 gm. daily for eight days. After this period, the drug was omitted for five days, when the same dose was readministered. Four days later, severe chills, a rise in temperature to 104°F. and pharyngitis developed. The white-cell count dropped from its previously normal level to 2000, with 200 granulocytes. Treatment consisted of the omission of thiouracil and the administration of vitamin C, 40 cc. of Pentnucleotide for one day, liver extract and sulfadiazine. Recovery occurred after ten days.

An additional fatality from agranulocytosis caused by treatment of the thyrotoxicosis with thiouracil has been reported by Kahn and Stock.[16] This patient received 0.8 gm. for two days, 0.6 gm. for forty-two days and 0.4 gm. for seven days, when pharyngitis, fever and agranulocytosis developed. Whole-blood transfusions, crude liver extract, Pentnucleotide, yellow bone-marrow extract and penicillin were utilized therapeutically, without avail.

Rubinstein[17] has recently reported a case of severe neutropenia following thiouracil treatment of carcinoma of the thyroid gland. Neutropenia developed after 0.8 gm. had been administered for one hundred and eleven days, when the white-cell count was 1700, with 1000 granulocytes. The drug was then stopped. Five days later, the white-cell count was 750, with 75 granulocytes and 30 myelocytes. At the height of the neutropenic reaction there was no fever or ulcerative lesions in the mouth or throat, but transfusions were given. Recovery gradually occurred in the subsequent four weeks. Sternal-marrow studies were done on the seventh, eleventh, fifteenth and twenty-ninth days following the onset of neutropenia. Differential counts of the sternal marrow showed marked depression of the myeloid series, with an inverse increase in the erythroid series. In addition, there was arrest of maturation of the myeloid series, as evidenced by complete disappearance of segmented neutrophils, basophils and eosinophilic and basophilic myelocytes and markedly depressed numbers of nonsegmented neutrophils and neutrophilic myelocytes. These findings were taken as indicating that the agranulocytosis was caused by arrest of maturation associated with myeloid hypoplasia.

Rose and McConnell[18] treated 37 thyrotoxic patients with thiouracil in doses up to 1.0 gm. daily and observed 2 cases of severe neutropenia associated with pharyngitis and fever. In the first case, the white-cell count dropped to 1200, with 336 granulocytes, after twenty-three days of treatment. The drug was stopped and Pentnucleotide was administered. Two days later, the white-cell count was 1850, with only 222 granulocytes. Full recovery occurred after eight days. One week later, the administration of 0.2 gm. of thiouracil daily for six days was followed by a drop in the white-cell count to 2400. The drug was again stopped. Beginning a month later, 0.2 gm. of thiouracil was administered for a two-month period, without subsequent neutropenia. In the second case, pharyngitis and fever developed after nine days, associated with a white-cell count of 2200, of which 1520 were granulocytes. Stoppage of the drug was followed by recovery after three days. Resumption of thiouracil therapy was attempted after one month but was followed by fever, lymphadenopathy and pharyngitis after 0.4 gm. had been administered. On this occasion the white-cell count remained normal, but the drug was omitted because of the other toxic symptoms. This patient had a previous history of allergy and iodine dermatosis. In addition to the severe reactions in this series, 14 patients with normal white-cell counts before thiouracil was given exhibited counts below 5000 within four to fifty-five days after institution of treatment.

In 6 of these patients, the count returned to normal in spite of the continued administration of thiouracil. Of the remaining 8 patients, 1 showed an initial transient leukopenia after ten days, with normal counts for seven months, while taking 1.0 gm. of thiouracil daily. At the end of this period, the white-cell count dropped to 2800. Further details were not given.

Nussey[19] treated 27 patients with toxic goiter with thiouracil in doses ranging from .05 to 0.6 gm. daily for periods ranging from three weeks to twelve months. White-cell counts were taken in all cases at intervals of one to several months while the patients were under treatment. Seven patients exhibited some degree of neutropenia or leukopenia during treatment, and in 2 cases initially low white-cell counts persisted or were intensified as the metabolic rate approached normal. In 1 case, the leukopenia was associated with a skin rash due to the drug, but in the remaining 6 cases no clinical symptoms of toxicity were noted.

Ferrer[20] has reported an additional fatality from agranulocytosis following the administration of thiouracil to a man of seventy with a toxic nodular goiter. The patient received 0.8 gm. daily for three days, 1.2 gm. daily for ninety-one days, 0.9 gm. daily for twenty-nine days and 0.6 gm. daily for seven days. The initial white-cell count was 9500, with 5700 granulocytes. The count gradually dropped to 5150, with 3350 granulocytes, during the first five days of treatment. Thereafter the white-cell count ranged from 5100 to 7400. Toward the end of the fifth month of therapy, the count was 1250, with 462 granulocytes. For the next two days the patient felt well, but on the fourth day a fever of 105°F. developed, and on the fifth day pharyngitis appeared. This progressed in severity, and the patient died on the seventh day. During this period, the white-cell count continued to decline and reached 450, with no granulocytes, on the day of death. Pentnucleotide and whole-blood transfusions were of no benefit. Penicillin was administered during the last twenty-four hours, without effect. Post-mortem examination showed nonulcerative pharyngitis, multiple substernal adenomas of the thyroid gland, generalized dilatation of the heart, hemorrhagic lobular pneumonia and hemoglobin nephrosis (probably due to transfusion reactions). The bone marrow showed moderate granulocytic hypoplasia, with decreased adult neutrophils.

This review of reported cases in which thiouracil has caused varying degrees of neutropenia indicates that there are three main groups of cases — first, those with transitory neutropenia, entirely asymptomatic and often confused with the mild neutropenia and corresponding lymphocytosis of toxic goiter; second, those with significant neutropenia, frequently associated with clinical symptoms, especially fever and pharyngitis, readily improving on stoppage of the drug and occasionally despite its continuation; and third, those with true agranulocytosis, corresponding in detail to the usual clinical syndrome of agranulocytic angina and often fatal.

The incidence of the first group of neutropenic reactions in all reported series occasioned little comment because spontaneous recovery usually occurred. Although ascribed by some authors to thyrotoxicosis rather than to thiouracil, these reactions seem clearly due to the drug, for three reasons. First, administration of the drug in these cases frequently produced a granulocyte count that was lower than the pre-treatment level. Second, omission of the drug was regularly followed by a return of the depressed white-cell count to normal. Third, the decreased granulocyte count often developed as the thyrotoxicosis receded. No bone-marrow studies in this group are yet available, but it is probable that a temporary depression of the myeloid elements in the bone marrow occurs. An example of the slight and passing nature of this reaction is illustrated in Table 4 (Case 5). In this patient with mild thyrotoxicosis, the administration of thiouracil resulted in leukopenia and neutropenia after one week of treatment. The drug was continued, and the white-cell count returned to pre-treatment levels within one week.

TABLE 5. *Occurrence of Reported Cases of Neutropenia and Agranulocytosis.*

SOURCE	CLASSIFICATION OF CASES*			DURATION OF TREATMENT PRECEDING GROUP 2 AND GROUP 3 REACTIONS
	GROUP 1	GROUP 2	GROUP 3	
				days
Astwood[4]		1	1	90, 37
Williams and Clute[8]	?	1	1	Several days, 42
Gabrilove and Kert[10]	1			16
Paschkis et al.[11]		1		240
Sprunt[12]	9†			
McGavack et al.[13]	3	1	1	6, 42
Himsworth[14]	?		1‡	Not given
Meyer[15]		1		54
Kahn and Stock[16]			1‡	51
Rubinstein[17]			1	111
Rose and McConnell[18]	14	2		9, 23
Nussey[19]	6	1		Not given
Ferrer et al.[20]			1‡	150
This series	1	3	1‡	8, 21, 24, 29

*Group 1 = transitory, asymptomatic leukopenia not requiring treatment or stoppage of thiouracil; Group 2 = neutropenia with symptoms usually requiring stoppage of thiouracil; Group 3 = agranulocytic angina.

†Some of these cases probably belong in Group 2, but not enough data were available for classification.

‡Fatality.

The group of asymptomatic and transitory neutropenias caused by thiouracil merge into the second or intermediate group of cases, which may also be transitory but have usually shown clinical symptoms. In these cases, the granulocytes have generally numbered less than 1000; the clinical manifestations have varied from mild to severe and have usually included some degree of fever, pharyngitis and lymphadenopathy. Recovery has invariably occurred, usually with omission of the drug but occasionally in spite of its continued administration.

Cases in the third group are characterized by complete agranulocytosis, severe clinical symptoms

and occasionally death. All patients in this group have been gravely ill but have had a recovery rate of 50 per cent.

The development of neutropenia and agranulocytosis following the administration of thiouracil is clearly not due to thyrotoxicosis, since these complications have occurred in patients without toxic goiter to whom the drug was administered as a metabolic depressant. Moreover, in many patients these deleterious reactions have occurred during remissions of the thyrotoxicosis induced by the drug.

Two other causative factors of the neutropenia have been postulated — namely, dosage and hypersensitivity. As regards dosage, one should consider both the size of the daily dose and the duration of administration. Thiouracil is not a cumulative drug, since its excretion is extremely rapid.[9] Nonetheless, a depressing effect on the bone marrow may be cumulative with long-continued though small daily doses, as exemplified by Case 1, in which fatal agranulocytosis occurred after the patient had received daily doses of 0.2 gm. of thiouracil for four weeks. Severe or fatal reactions have occurred at dosage levels ranging from 0.2 to 2.0 gm. daily after six days to eight months. In many cases the dosage was appropriately reduced as the thyrotoxicosis abated, without preventing the onset of severe neutropenic reactions. The evidence is adequate that the dosage-time factor is not a controlling influence in the etiology of thiouracil neutropenia and agranulocytosis.

The factor of hypersensitivity in the production of neutropenic reactions has long been considered significant.[21] Thiouracil definitely falls into the group of drugs that produce typical allergic manifestations — namely, drug fever, urticarial and other types of skin eruptions and reproductions of toxic symptoms with readministration in small doses. Chemically, thiouracil is closely related to barbital or diethyl barbituric acid, a compound whose derivatives have occasionally though rarely been reported to cause agranulocytosis.[22, 23] With this allergic background, the unpredictability of the toxic manifestations of thiouracil becomes clearer.

Whereas chemically thiouracil is nearest to the barbiturates, toxicologically it most closely resembles the sulfonamides. Many of the latter compounds similarly have antithyroidal effects like those of thiouracil but of lesser degree. This similarity is seen not only in the usual toxic reactions of drug fever, neutropenia and dermatitis but also in two more unusual ones — first, the ability to recover from severe neutropenia despite continuation of the causative drug, and second, the capacity of becoming desensitized to the drug with the repeated administration of small doses. Nixon, Eckert and Holmes[24] found that in 3 patients with agranulocytosis or severe neutropenia following the use of sulfadiazine, continued administration of this drug in large doses did not prevent complete recovery. Williams and Clute[3] have reported a similar experience with a case of thiouracil neutropenia with a granulocyte count of 640. Recovery occurred in spite of the continued administration of the drug.

Desensitization to thiouracil has been noted by several authors. Sprunt,[12] for example, found that its readministration in small doses after a neutropenic reaction was not often followed by recurrence of the neutropenia. Similarly, Rose and McConnell[18] were able to desensitize 2 patients so far as the bone marrow was concerned by readministration of thiouracil after marked neutropenic reactions. Readministration of the drug is followed by phenomena of sensitivity oftener than by desensitization, but further study on this point is needed. If there is a true analogy with the usual protein type of allergy, attempts at desensitization should be made at extremely low dosage levels.

Whether the depressed function of the bone marrow is due to allergy or to overdosage, the actual production of neutropenia either is the result of arrest of maturation at the promyelocyte stage or occurs through direct destruction of white cells beyond the promyelocyte state. Bone-marrow studies have been reported by Rubinstein[17] and by Ferrer, Spain and Cathcart,[20] and in Case 1 of this series. The findings in all cases have been the same, except that in ours the bone marrow showed large numbers of disintegrating forms as possible evidence of a destructive effect of thiouracil. Moreover, a similar destruction of granulocytes may occur in the circulating blood, a process suggested by Lawrence[25] as a mechanism for the leukopenia.

Prevention and Treatment

The foregoing review of our own and reported cases indicates clearly the difficulties that surround the continued safe administration of thiouracil. No general rule can be laid down that will guarantee freedom from serious hematologic reactions. Dosage, duration of treatment, constant or intermittent therapy, associated clinical phenomena and premonitory symptoms have not proved safe guides. Serious reactions have occurred at both high and low dosage levels, with short and with long treatment and with both constant and intermittent administration of the drug. Premonitory symptoms are rarely present, and one severe neutropenic response has occurred without associated fever or ulcerative pharyngitis.[17] Experience with hematologic reactions caused by drugs indicates that uneventful administration of a drug in normal doses for various periods of time in no way precludes the appearance of sudden unexpected sensitivity of the bone marrow.[26]

One must therefore balance the unpredictable nature of the toxic effects of thiouracil against the seriousness of alternative methods of treatment of thyrotoxicosis. The available alternates are pro-

longed iodine administration, irradiation and thyroidectomy. Iodine administration is adequate in only a small percentage of cases, and irradiation is slow and unpredictable. Surgery is effective and quick in controlling a large percentage of cases. Thiouracil compares favorably with surgery in speed and certainty of treatment, but the expected fatality rate from thyroidectomy ranges from 0.5 to 2.0 per cent, and thiouracil has not yet resulted in mortalities of this magnitude, although the incidence of toxic reactions from the drug[27] is far greater than that of deaths following surgical extirpation. Furthermore, surgical deaths are most frequently encountered in the severely toxic cases, whereas thiouracil may cause fatal reactions in mildly toxic cases.

The proper treatment of thyrotoxicosis with thiouracil offers an opportunity to avoid the mortality associated with thyroidectomy in severely toxic cases. Thiouracil is capable in most such cases of reducing the high metabolic rate to a normal level and thus permitting one-stage thyroidectomy without danger of thyrotoxic crisis. Thiouracil is similarly useful as the sole agent of treatment in cases with an inadequate response to iodine therapy in which surgery is not feasible because of the physical status of the patient, because adequate surgical facilities are not available or because the patient refuses operation. Finally, thiouracil has a possible use in the management of persistent or recurrent thyrotoxicosis when adequate thyroidectomy has been performed without complete control of the disease or when there is unsatisfactory remission with iodides. The routine use of thiouracil as a substitute for iodides in the preparation of patients for thyroidectomy requires more study.

Thiouracil is definitely contraindicated in the continued management of patients with large or nodular goiters. The drug eventually controls the thyrotoxicosis, although taking longer to do so than in cases with moderate-sized thyroid glands, but leaves the gland in such a vascular state that removal is rendered more difficult. Toxic nodular goiters should be surgically removed because of the growth hazards of the nodule, both through the production of neoplastic lesions and by pressure.

Whatever the final position of thiouracil in the treatment of toxic goiter, it is clear that there can be no admissible use of the drug without thorough supervision of the patient. No false reliance should be placed on either dosage or duration of therapy. Once treatment is begun, white-cell counts must be made at least three times weekly, with differential counts when the total count drops below 5000. The occurrence of pharyngitis and fever is an unsafe guide to the blood picture, since these may develop relatively late in the course of the disease; indeed, in one fatal case agranulocytosis preceded these symptoms by several days.

These proposed safeguards for the use of thiouracil are indispensable because no proved protective measures are as yet available. In animals, it has been established that a component of vitamin B complex is essential for the prevention of nutritional cytopenia.[28] This component has been variously called "folic acid," "vitamin M" and "vitamin B_c." It is abundantly present in yeast, fresh liver and certain crude liver extracts. These prevent but do not always cure nutritional cytopenia. Spicer and his co-workers[29] have shown that sulfonamide-induced neutropenia and agranulocytosis in rats can regularly be prevented by addition to the diet of liver extract or yeast or of crude folic acid preparations from these foods. Daft and Sebrell[30] have shown that preparations of crystalline folic acid correct this sulfonamide-induced neutropenia after it has been established.

A similar approach has recently been suggested for the prevention of the neutropenia usually induced by thiourea in rats.[31] Liver or folic acid was found to be successful in preventing this state. The application of this knowledge to thiouracil neutropenia in man remains to be elaborated. In monkeys suffering from nutritional cytopenia, however, cure with these materials is not always satisfactory,[28] since the animals enter an irreversible phase if the deficiency is allowed to progress too far. Thiouracil agranulocytosis in man, with a mortality rate of 50 per cent, is characterized by many elements of this irreversibility, so that treatment should be applied early and vigorously. It should consist of early omission of thiouracil, early institution of penicillin therapy as soon as it is suspected that spontaneous remission will not occur with omission of the drug alone, the use of folic acid, if available, or large amounts of liver or yeast and other measures that may be useful in agranulocytosis, such as the giving of Pentnucleotide and transfusions.

Summary and Conclusions

Of 61 patients with thyrotoxicosis and 1 with heart disease treated with thiouracil, 3 developed moderate to severe neutropenia and 1 developed fatal agranulocytosis.

A review of all reported cases of neutropenia and agranulocytosis caused by the thiouracil is presented.

Various causative mechanisms of the toxic effect of thiouracil on the bone marrow are discussed.

Hypersensitivity is considered more significant than the dosage-time factor.

Thiouracil depresses the bone marrow, causing arrest of maturation at the promyelocyte state and possibly destruction of cells beyond this stage.

The indications for thiouracil and safeguards for its usage are described.

The prevention and treatment of thiouracil neutropenia and agranulocytosis are discussed.

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THE CLINICAL SIGNIFICANCE OF DATA ACCUMULATED IN THE MEDICAL CARE OF YOUNG WOMEN

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CLINICIANS have not shown great interest in the study of the so-called "normal." The physiologists have made useful contributions, but these have not, for the most part, reached the clinician in such a way that he is led to apply the knowledge thus acquired. A review of the literature since 1918 reveals less than forty references dealing with the subject of normal physical findings as related to clinical medicine. A few of these deserve listing.[1–6] The Selective Service findings reported and publicized by Rowntree[7] have brought up many questions about supposedly normal and supposedly healthy men. Members of the Grant Study at Harvard University have made some contributions to the study of normality in recent years.[8–11] Ivy[6] has recently made a most helpful report on this subject. In spite of these scattered reports, it is still true that medicine in all its branches is chiefly concerned with major departures from a supposed norm — gross pathology and lesions that lend themselves to dramatic curative measures. But the expansion of knowledge in bacteriology and its application to public-health practice suggest that in the future the most valuable contributions of medicine will be along the lines of preventive measures. From this concept it seems a logical step to study carefully the normal with all possible variations, especially as they relate themselves to the clinician's problems. This study will lead to knowledge of the ideal base line from which preventive medical measures can be planned. And as variations in the normal are learned in detail, it may become possible to detect the exact point at which a given disease has its onset — knowledge that is badly needed for understanding and prevention.

If the foregoing is true, there is distinct help to be had from the day-by-day accumulation of data of a college health service. Here may be found the materials with which to make tables of variables in physical and physiologic findings in young men and women of this particular age group. It is recognized that these persons comprise a selected group who have doubtless received better food and better protection from disease and accident than has the general population; yet there may be found in such data a wealth of material from which to learn the

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range of the probable ideal normal toward which to work to attain maximum health for the individual. Such knowledge may also prove useful in preventing diagnostic errors due to too narrow an interpretation of laboratory findings. One of the purposes of this paper is to point out the wide ranges of physiologic variation that are possible among normal young women. The information given below is intended to illustrate these ideas and to suggest the clinical use of this knowledge. The material is drawn from observations made in the routine work of the Department of Health Education of Radcliffe College from 1941 to 1944.

Blood-Pressure Readings

We have been impressed with the number of young college women who have been told by physicians that they are suffering from low blood pressure. Such women have usually presented themselves to the physician complaining of fatigue. Our study of such complaints has convinced us that the causative factors associated with fatigue are usually lack of sufficient rest and exercise, stress of the emotional struggle that often accompanies the change from adolescence to adulthood, and the strain, real or imagined, of academic life. Seldom, if ever, is it found that a low blood-pressure reading and fatigue are directly related. Occasionally, following a severe infection or in the presence of a marked iron deficiency, such a reading is temporarily recorded. In most cases, however, the complaint of fatigue disappears when the factors outlined above are properly handled, yet the blood pressure remains low.

There is not much material in the literature that bears directly on this subject. Fisher and others[12–14] published careful tabulations of insurance-company figures. Alvarez[15] objected to such statistics because they represent only accepted applicants for life insurance. He[16] was at one time deeply interested in collecting blood-pressure readings taken on young men and women at the University of California. He found that the women's readings were more uniform than the men's and averaged 11 mm. lower. In 1923, Symonds[17] presented a huge number of blood-pressure readings of women of all ages that had been collected by life insurance companies. His figures are higher for the same age group than those of Alvarez and higher than those presented here. The objection raised by Alvarez is of course applicable. The more recent article of Robinson,[18] in which he thoroughly reviewed the literature and discussed the whole question of hypotension is of significance.

The blood-pressure readings in 1000 college women between the ages of sixteen and twenty-two were recorded, and the findings are presented in graphic form (Fig. 1), as suggested by Alvarez.[15] This graph shows the distribution of the systolic and diastolic readings in millimeters of mercury, taken with the armband sphygmomanometer with the student in the sitting posture. All these young women had had a complete medical history and a careful physical examination, including hemoglobin determination, urinalysis and x-ray examination of the chest. In none was anything outside the

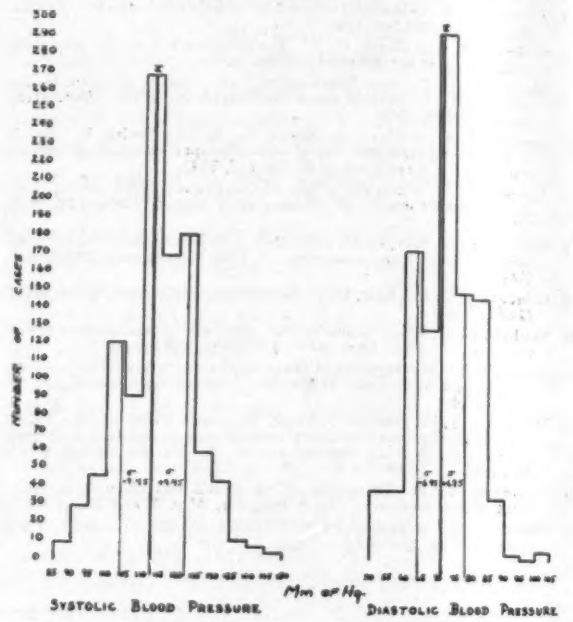

Figure 1. *Blood-Pressure Readings in 1000 Young Women.*

accepted range of normal detected. No student complained of faintness, dizziness or syncope at the time the blood-pressure reading was recorded, nor could such a history be elicited.

As the graph shows, the systolic pressure averaged 113, and the diastolic 71. It is of interest that there were seventy-eight systolic readings of 100 and under, and seventy diastolic readings of 60 and under, without any subjective symptom or clinical sign of so-called "hypotension." This record leads us to agree with Robinson[18] that there is probably no such clinical entity.

White-Cell Counts in the Menstrual Cycle

Not infrequently the physician in college medical practice is called on to decide how to handle the complaint of pain in the right lower quadrant of the abdomen in a young woman who is menstruating. This problem is almost always a complicated one regarding diagnosis and treatment. In our experience, the management of such cases is made more difficult by an elevated white-cell count, which might easily be attributed to menstruation. The finding of a normal-appearing appendix at operation on such a subject has raised the question what one may reasonably expect as physiologic variation due to menstruation. Hence, an attempt was made to ascertain the range of the white-cell count during the menstrual cycle.

Authors writing on this topic have come to a variety of conclusions. The standard textbooks

are not particularly helpful, as shown by Best and Taylor's[19] statement that leukocytosis occurs during menstruation and by the failure of Wright[20] and Stitt[21] to mention any change whatever in the white-cell count at such a time. Curtis[22] says that shifts in white-cell counts should not be overemphasized because of the effect of exercise and digestion in causing physiologic variations. Ehrenfest,[23] writes, "Investigators disagree in regard to a characteristic leukocytosis in the premenstrual week." Menkin,[24] in his work on changes in white-cell counts in relation to tissue damage, suggests that there might well be a premenstrual rise in leukocytes if the Smiths[25] are correct about the toxicity of menstrual fluid.

Gumprich,[26] writing in 1914, reported that leukocytes reached their maximum on the first day of flow, after which there was a sharp drop. Hayem[27] and Dirks[28] both believe that there is a definite increase in white cells during menstruation. Blumenthal[29] reports a decrease in white cells during menstruation. Novak[30] summarizes these reports in his monograph and concludes that there is no clear picture of what effect menstruation has on the white-cell count.

Two physiologists, Garrey and Bryan,[31] made a careful report in 1935 that is extremely helpful in evaluating physiologic variations in white-cell counts due to age, posture, random activity, strenuous exercise, digestion, climate, pregnancy and emotional states. The report was brought up to date in 1943 by Sturgis and Bethell.[32] Both these reports also deal with technical errors in such determinations and present knowledge of the mechanism utilized by the body in the distribution of white cells in response to physiologic changes. Neither of these reports speaks of menstruation and its physiologic effect on the white-cell count.

In Figure 2 is presented a graph of the total white-cell counts of normal women plotted against the day in the menstrual cycle on which the count was taken. One hundred and five of these counts were furnished through the courtesy of Dr. George Minot of the Thorndike Memorial Laboratory, Boston City Hospital, where they were done by Miss Elizabeth King and Miss Geneva Daland on healthy women who were technicians in the laboratory. One hundred and fifty-six of the counts were made on well college freshmen at the time of the routine physical examination on arrival at Radcliffe College. Complete medical histories and careful physical examinations were done at the same time, so that counts of any student with detectable disease could be excluded.

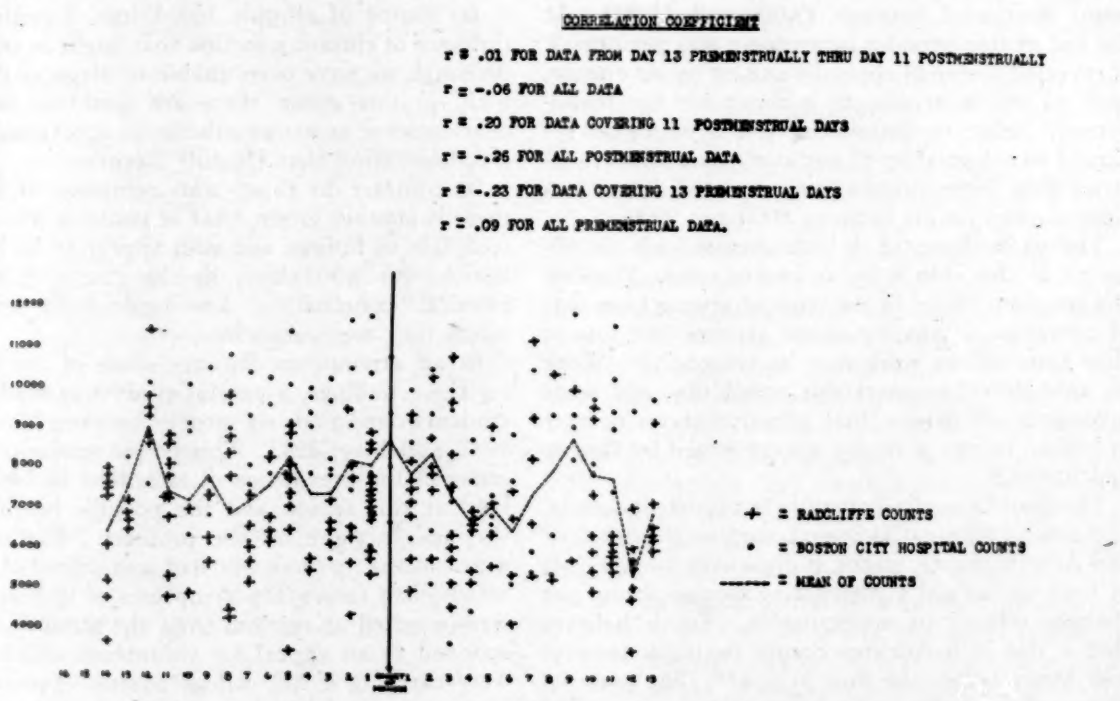
CORRELATION COEFFICIENT
r = .01 FOR DATA FROM DAY 13 PREMENSTRUALLY THRU DAY 11 POSTMENSTRUALLY
r = -.06 FOR ALL DATA
r = .20 FOR DATA COVERING 11 POSTMENSTRUAL DAYS
r = -.26 FOR ALL POSTMENSTRUAL DATA
r = -.23 FOR DATA COVERING 13 PREMENSTRUAL DAYS
r = .09 FOR ALL PREMENSTRUAL DATA.
+ = RADCLIFFE COUNTS
• = BOSTON CITY HOSPITAL COUNTS
------ = MEAN OF COUNTS

FIGURE 2. *Variations in the White-Cell Counts in Menstruation.*

Because of the slightness of the shifts in the counts it does not appear that exercise and digestion are significant. Furthermore, if the possibility of technical error is taken into account, this record of counts does not seem to show any distinct trend at any particular time in the menstrual cycle. The extremely low counts were repeated and remained approximately the same. The persons with counts under 4000 must be followed with a serious granulocytopenia in mind, such as that in the case reported by Jackson, Merrill and Duane.[33] The few counts above 10,000 may have various explanations worth

bearing in mind for aid in the diagnosis of a surgical abdomen. After errors in technic are eliminated, one must consider the physiologic variations due to pain, as pointed out by Wolff[34] in a study of women in labor. Not enough cases have yet been studied to warrant conclusions, but experience in the Radcliffe Medical Office has been that the pain of dysmenorrhea does not ordinarily produce leukocytosis. An occasional case, however, is seen such as that of a nineteen-year-old student with a normal menstrual history except for slight dysmenorrhea on the first day of flow who reported to the office because of pain in the right lower quadrant of the abdomen on the third day of menstrual flow. When the white-cell count was found to be 19,000, the student was referred to a surgeon, who had her hospitalized. The surgeon kept her under observation for thirty-six hours, during which time the count fluctuated between 19,000 and 23,000. At the end of this period a laparotomy was performed. It revealed a normal appendix and no pelvic disease, such as endometriosis, to account for the leukocytosis. After operation the white-cell count returned to a normal level, and during a normal menstrual flow three months later repeated determinations showed counts between 8000 and 9000.

The explanation of a leukocytosis such as observed in this case is by no means clear. Possibly the emotional state of the student arising from fear of operation or anxiety about expense and loss of time from college work may be responsible. Work on animals[35, 36] suggests this possibility, and some investigators[37] believe that affective states operate in human beings, a theory also proposed by Garrey and Bryan.[31]

The present method of study is admittedly crude, and careful differential counts, such as the Schilling and Arneth counts, might, if done over long periods of time on normal menstruating women, bring out changes related to menstruation. Smith believes that a rise in leukocytes occurs twelve to twenty-four hours before the flow begins.[38] The material presented here should be followed by larger numbers of similarly taken white-cell counts before the final word is said on the physiologic variation in counts during menstruation. For the practical purpose of differential diagnosis, however, there is seen in this study no suggestion that the white-cell count undergoes a physiologic shift at any time in the menstrual cycle. The clinician and the surgeon must continue to make the diagnosis of a surgical abdomen on the basis of the history and physical findings. It seems a fair conclusion that, barring an occasional subject whose excessive response to a "crisis" produces a leukocytosis, an increase in white cells beyond 10,000 per cubic millimeter in a menstruating woman has to be explained.

Anemia and Fatigue

When a young woman complains of fatigue, one of the first steps in diagnosis and treatment is to obtain a red-cell count and a hemoglobin determination. Often these values are below the textbook norms: the hemoglobin reading is about 70 per cent on the Sahli scale, and the red-cell count is below 4,500,000. The physician then prescribes iron by mouth, and expects that the sensation of fatigue will yield to the establishment of a high hemoglobin level.

Our experience with young college women who complain of fatigue and who present the laboratory findings described above has not been consistent with this expectation. First, a rise in the hemoglobin level to what is considered normal does not by any means always relieve the fatigue. Second, there are many cases in which proper therapy as outlined by Castle[39] does not result in a change in hemoglobin level. Care has been taken, of course, in the treatment of these cases to be sure that there is no source of chronic blood loss, digestive disturbance or chronic infection that might be relevant. Although we have been unable to diagnose them as such, in this group there are doubtless cases of deficiencies of necessary substances other than iron—a consideration that Heath[40] discusses.

In contrast to those who complain of fatigue, there is another group, that of students who do not complain of fatigue and who appear to be in good health, yet who show, in the course of routine physical examination, low hemoglobin levels of which they were unaware.

In an attempt to discover some of the reasons for these findings, a careful study was made of 12 students during the six months between November, 1942, and May, 1943. This period was selected because of the prevalence of infections in New England at this season and the possible bearing that they might have on the problem. The students were not among those who had complained of fatigue or who had shown any symptoms of ill health, but were selected at random from the number who responded to an appeal for volunteers. All of them were carrying a full college course. Ten of them also carried a fairly heavy load of student, social and war activities.

A detailed history of each student was taken in the attempt to discover any possible source of iron deficiency prior to this study. The students were given a set of questions, to be answered by their mothers, relative to the presence of anemia in the mother during pregnancy, serious childhood infections or childhood feeding problems that might be relevant. A full record was made of adolescent medical histories for information concerning errors in diet, menstrual disturbance or any chronic diarrhea, infection or blood loss, however slight. A thorough routine physical examination, such as is given to all entering college students, was included. A gastric analysis was not done, although one would be desirable, since, as many authors have pointed out,[41–43] proper iron absorption depends on the acidity of the gastric contents.

During the period of the study each volunteer reported every two weeks to have a sample of blood taken from a vein. A Sahli hemoglobinometer was used.* The same tube was employed for each reading. At each of these visits a brief history was taken, with special reference to the complaint of fatigue, diet irregularities, any unusual stress and strain that resulted in insufficient rest, physical exercise, menstrual irregularities and intestinal upsets. From each sample of blood a red-cell count and a hemoglobin determination by the Sahli method were made. The findings were plotted on a graph against the dates of the students' visits (Fig. 3). From these

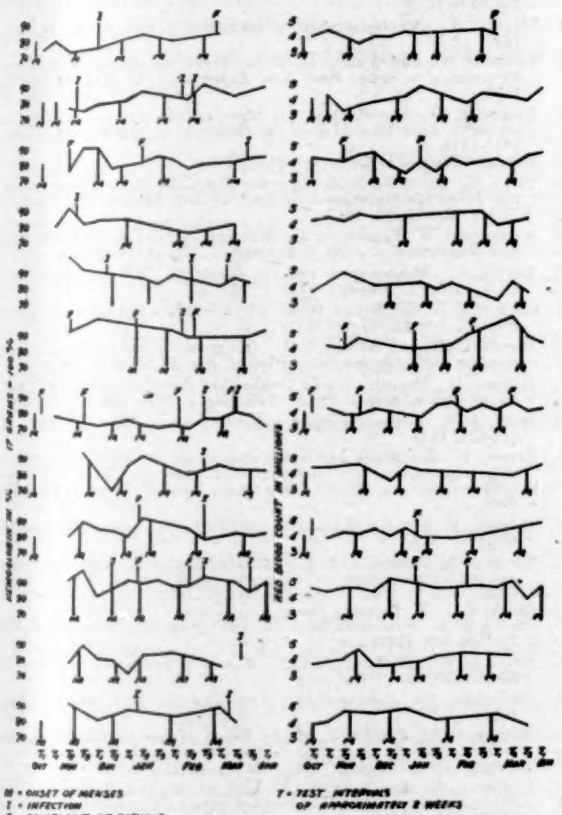

FIGURE 3. *Variations in the Hemoglobin Levels and the Red-Cell Counts in 12 Young Women.*

graphs an attempt was made to find variations that might be correlated with any of the facts elicited from the histories — especially, of course, the complaint of fatigue.

The case histories furnished what must be a fairly usual assortment of stories. Among the parents of the 12 volunteers, two mothers and one father gave a history of anemia. Two of the students had been feeding problems, and 3 had had a serious infection in early childhood, — 2 cases of scarlet fever and 1 of pneumonia. The adolescent histories up to the date of the study included 4 cases of poor eating habits, — that is, no breakfast, many sandwiches and soft drinks and too little meat and milk,— 7 of three or more moderately severe head colds each winter, 1 of chronic gastric upsets and 4 of intermittent bouts of diarrhea not considered serious enough to require medical attention. The single menstrual disturbance was an irregularity that did not result in excessive blood loss. One student in 1941 had had a basal metabolic rate of —17 per cent, which, after thyroid therapy, returned to within normal limits. Four students gave a history of easy fatigability prior to the period of this study, and 7 complained of fatigue at different times during this period. These complaints, however, were not spontaneous but were elicited only by questioning.

The striking fact is that, although at some time or another during the study seven of the graph curves showed hemoglobin values of 70 or 80 per cent, these occurrences did not coincide with the times at which the complaint of fatigue was present. Making allowance for experimental error, there are still no significant variations in the curves described by the records of these levels, and no relation between a red-cell count and hemoglobin slightly below normal and fatigue, menstruation or infection. Infections during this period of study were few and not severe, consisting of 1 case of German measles, 1 of mild otitis media and the usual run of upper respiratory disease and what is loosely termed "grippe." Menstruation has already been shown by workers in this field to produce no definite variation in the red-cell count and hemoglobin values provided that other factors, such as dietary deficiency and infection, are absent.[26, 44, 45] This fact is emphasized in the graphs presented here.

In an analysis previously made by me of the diet of the average college student, diet histories covering four complete days for each student were taken in minute detail from thirty students. The North End Diet Kitchen of the Massachusetts General Hospital found that every one of these diets was deficient in iron and that all but two were deficient in thiamine chloride, according to present standards. It is reasonable to infer from this, therefore, that the diets of the 12 students in the group under discussion — 4 of whom gave frank histories of inadequate and poorly planned nutrition — may have shared these deficiencies. In view of Heath and Patek's careful analysis[40] of present evidence of the amount of iron the body needs daily to maintain its optimum level, the dietary lack of iron in young college women is probably not highly important. It is possible, however, that this is a factor in the otherwise inexplicable low hemoglobin levels in some students who have no clinical complaints, since there is a greater demand for iron in young women because of menstrual blood loss.

From this study it is concluded that since red-cell counts and hemoglobin levels slightly lower than normal are apparently not related to fatigue, menstruation or infection and produce no other symptoms, the body is able to manage efficiently with what has been considered to be less than the normal blood level. It may be wise, however, to treat this

*Sahli standards were calibrated so that a hemoglobin of 100 per cent was equivalent to 17 gm. per 100 cc. of blood.

condition to prevent an iron deficiency at a later date when, as Heath[46] suggests, the body demands more available iron — as in pregnancy. Iron-deficiency anemias due to blood loss or to severe infection do, of course, produce a complaint of fatigue that responds dramatically to the proper use of iron by mouth. There is, nevertheless, much that is apparently still unknown about the human body's need for and use of iron. This study indicates the need for further research in the great problem of fatigue.

* * *

These three short studies are presented to emphasize the value of analysis of normal findings and their variations. Such knowledge will be helpful, as Alvarez[15] points out, "to spare patients pain and needless treatment" and will add to the general understanding of so-called "normal." Although the findings presented here do not corroborate widely held opinions regarding the significance of certain levels of blood pressure and hematologic values, it is through the pursuit of such inquiries as this that preventive medical measures and methods of detecting the onset of disease may eventually be learned.

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MEDICAL PROGRESS

MENSTRUATION, ITS DISORDERS AND THEIR TREATMENT*

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CONSIDERATION of menstruation is organized as follows: factors in normal menstruation, character of normal menstruation, disorder in frequency of flow, disorder in duration or amount of flow, disorder in frequency, duration and amount of flow and treatment.

FACTORS IN NORMAL MENSTRUATION

To produce the physiologic shedding of the mucosa at the conclusion of a sterile cycle, two separate endometrial processes are closely integrated. One is the cytologic development of this tissue from a proliferating to a secretory or functional membrane, which then gradually changes to a predecidua. The second endometrial process, distinct from the first, although usually associated with it, is the establishment of the bleeding potential, the activation of which causes the destruction of the superficial portion of the predecidua.

The Predecidua

The cellular changes marking the sequences in mucosal development during the menstrual cycle have been frequently described since Hitschmann and Adler's[1] time (O'Leary,[2] Bartelmez[3] and Rock[4]). Growth of what is left after deciduation of the upper layers proceeds to full proliferation of the tissue. After ovulation, this quickly changes into the functional endometrium. Finally, during the last premenstrual week, this is transformed into the thick compact layer of the predecidua. Proliferation is known to be the effect of estrogen from the growing follicles. Secretion is the result of the addition of gradually increasing amounts of progesterone from the young corpus luteum. The predecidua is the result of the prolonged action of progesterone and estrogen and represents the limited extent to which the imperfect corpus luteum of futile ovulation can transform the lining of the uterus into the decidua of pregnancy, the full blossoming of the endometrium.

The Bleeding Potential

What is the nature of this obscurely termed "bleeding potential"? It is a "quality" not a "thing." As yet it is known only in action, not in being. Considering Markee's[5] observations and the Smiths's[6] biochemical findings, it seems best described as the susceptibility of highly differentiated arterioles to products of endometrial catabolism. This ability to bleed on the part of the uterine mucosa frequently is normally established in the primate endometrium without the cytologic changes that produce the particular function of the tissue. That is because the potentiality to bleed is initiated in the endometrium by the estrogens only. To be sure, the follicular hormone, as well as its two commonest derivatives, also stimulates proliferation of the endometrium; and usually these two functions of estrogen — growth of endometrium and development of bleeding potential — are ambivalent; but often they are not. So, even in the absence of pathology, bleeding sometimes occurs from a hypoplastic mucosa. The bleeding potential, although induced solely by the estrogens, is enhanced not only by continued action of an estrogen but to a greater extent by action of succeeding progesterone, especially if this is accompanied by an estrogen. The combined influence of the two hormones establishes the ability to bleed as a normal property of the predecidua. It must be remembered, however, that progesterone is not essential to the process of flow and that this frequently is evolved in the nonsecretory, merely proliferative, endometrium.

In those subprimate mammals in which, as in human beings, the corpus luteum is formed whether or not the egg is fertilized, the endometrium proceeds, as in women, from proliferation to formation of the predecidua; but the useless secretory tissue is partly shed and doubtless partly reabsorbed without the loss of blood. That this endometrial growth to a predecidua can take place in human beings without the second process — the synchronous development of the bleeding potential — is an unlikely possibility. Hence, in man disappearance of the predecidua without activation of the bleeding potential is not to be expected. Among several thousand patients in whom biopsies of the endometrium were studied, I have seen only one case in which a full secretory endometrium was changed to a subsequently proliferating tissue without a recognizable intercurrent bloody flow. As the patient had long been amenorrheic and was being treated for the condition, it is hard to believe that appreciable menstruation was either unobserved or denied. Occasionally there is found a pregnancy that starts after several months of amenorrhea and is thus of shorter duration than the absence of flow.

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Failing fertilization, would such a case be one of occult ovulation and corpus-luteum formation, or would flow have terminated the amenorrhea two weeks after rupture of the follicle? I do not know. One should be mindful, however, of extreme hypomenorrhea, that is, cyclic catamenia of only a few hours' duration, which is discussed later. This differs by only a few cubic centimeters of blood from complete failure of the bleeding potential to develop while the endometrium grows.

Activation of the bleeding potential is dependent on a critical change in the absolute or the proportional amounts of the various estrogens. Such critical change may occur with prolonged absorption by the blood of the estrogens from active growing follicles or from injected or ingested material. It is also found when a sufficiently high concentration of estrogenic substances in the blood is reduced after cessation of further increments from follicles or from medication. The critical change is also made when progesterone that has quickly followed or has been active concurrently with an estrogen is withdrawn. This last condition is typified by normal menstruation. Clinical evidence is mounting that activation of the bleeding potential also occurs when prostigmin evokes hyperemia of the endometrium. Does this drug merely lower the threshold of susceptibility of the local vascular system to the mysterious agent, a product of the catabolism of the endometrium[6] which starts the bloody destruction of the mucosa? Markee[7] has given an enduring classic description of how the bleeding starts in the monkey. There is every reason to believe that the process in human beings is quite similar. Markee states:

> Menstruation was studied microscopically in intraocular endometrial transplants in over three hundred cycles. The following sequence of events occurs in both ovulatory and anovulatory cycles, following castration, after injections of oestrin and after spinal transection. The superficial two thirds of the transplant, supplied by coiled arteries, becomes completely anemic. Four to twenty-four hours later circulation temporarily resumes in single arterial fields (the remainder of the transplant remaining anemic) and almost immediately blood escapes either from a capillary, or from an arteriole. It usually escapes from only one point and a hematoma may form. Occasionally it oozes for a short distance along one of these vessels, in which case a hematoma forms more slowly. Hematomata resulting from rupture of a vessel form and begin to discharge in one to twenty-five minutes, while those formed by diapedesis may persist for thirty-six hours. There is an occasional reflux of blood from a vein whose capillary bed is either constricted or destroyed. Single hemorrhages last from six seconds to twenty minutes. They are arrested by contraction of the appropriate coiled artery or its branch. Blood from these primary hemorrhages seldom clots. Fright at this stage causes, within fifteen to twenty-five seconds, reopening of the arteriole, which for five to fifteen seconds delivers blood that promptly clots. In many cycles, congestion and nearly complete stasis precede the anemic stage by 2 to 4 days.

Nonhormonal Factors in Bleeding

Although endometrial bleeding in the absence of local pathology may be dependent for its occurrence on the ovarian hormones, it is surely prolonged or increased by other than hormonologic agents. Among possibly modifying factors, one should note particularly the clotting qualities of the blood and the nature, especially the rapidity, of the tissue-repair processes. On these doubtlessly depends the permanent closure of the spiral arterioles, which are laid open to the uterine cavity when denudation occurs, although, as Markee[7] has noted, cessation of bleeding is first accomplished by recontraction of the vessel. Venous congestion, as well as inflammatory hyperemia, increases the flow. Contraction of the interlacing uterine muscle bundles probably helps to stop the loss of blood from the exposed and broken vessels by constricting the uterine arteries. Elements of diet or hygiene that may affect any of these processes should be included, although in a subordinate position, among the factors giving expression to the bleeding potential.

Character of Normal Menstruation

Many forms of catamenia, because they are found in healthy women, must be considered normal, although they differ widely from what may be called the pattern of perfect menstruation. Ideally the flow would occur only two weeks after ovulation; and ovulation would start only and always at puberty, at about the age of thirteen; and after puberty it would unfailingly occur periodically, except during pregnancy and lactation; and it would abruptly cease at a definite age, perhaps in the forty-fifth year. Ideally, too, the menstrual flow would be painless, persist for a reasonable stated period and be moderate in amount. Unfortunately such a complex mechanism, involving so many factors, functions thus ideally for not more than a few months at a time, and then in only comparatively few women.

Puberty is a phase, not a moment, in sexual development. It is during, not at, puberty that flow ordinarily starts. It may appear early or late in the period of sexual maturation. Puberty is the season during which the process of follicular development that has been in operation in the ovaries since before birth reaches fulfillment of function, ovulation. Although follicles in varying numbers approach the rupture stage, only an occasional one at irregular intervals is at first likely to complete the process. Thus there are, aperiodically, sufficient amounts of estrogen either to evoke full proliferation of the endometrium or to develop therein the bleeding potential. As has been said, this may be activated and bleeding ensue at equally irregular intervals by the critical breakdown of this estrogen alone, such as always occurs in the presence of progesterone but may take place without it. If the supply of estrogen is small, bleeding may be absent for many months. Then again, ovulation, and hence menstruation, may be rhythmic almost from the beginning. It may be said that, normally, puberty has been achieved when the process of ovulation has

been established, in that eggs ripen and are released at intervals characteristic of the human species. Furthermore and for obvious reasons, the term "normal menstruation" should be limited to that which follows ovulation.

Periodicity of Menses

Growth of follicles, which produce estrogen, evokes the bleeding potential; "withdrawal of hormonal support, with its accompanying change in endometrial metabolism and 'toxin' formation,"[8] precipitates the bleeding itself; but only the corpus luteum gives the bleeding true periodicity. This is so because the human corpus luteum functions for about two weeks. During these two weeks its specific secretion, progesterone, while enhancing the bleeding potential already inaugurated by estrogen, also inhibits its expression, probably by its influence on estrogen metabolism. Part of this time, increasing concentrations of estrogen in the blood have been augmenting the suppressed menstrual urge. With the decadence of the corpus luteum toward the end of the fortnight, the supply of follicular estrogen and of progesterone diminishes, inhibition is removed, and the bleeding potential is activated.

The corpus luteum, probably by means of progesterone, is also responsible for the regression that is common to all intact partly ripened follicles. When its dominance ends after the two weeks of its function, many other nonatretic follicles start to mature. Ordinarily, during the menarche, after about two weeks, one of them ripens, ruptures and forms another luteal gland. Thus is periodicity given to recurrent flow by the corpus luteum.

In the absence of ovulation, so far as is known, the corpus luteum does not form. The fortnightly inhibition of the bleeding potential is absent, as well as the repression of follicular growth. Follicles grow and regress irregularly; estrogen is produced, at times in large quantities, at times in small. The bleeding potential is developed and activated in the presence of an abnormally high estrogenic titer or of sudden decreases in the amount present, but without reference to time. Thus there is aperiodicity in the recurrent flow because of the absence of the corpus luteum.

Length of normal cycle. First, what may be considered neither too many nor too few periods? Somewhat misleading are our three terms for normal uterine discharge — menses, menstruation and catamenia, indicating, by derivation, "monthly flow." Never for long do cycles conform to the unnatural but civilly essential calendar month. With the lunar month of almost 29.5 days they are in much closer accord; but in no woman are the menstrual cycles of constant length however frequently they may approach this rhythm of the moon. In applying definitions to this subject of normal cycle-lengths, any essayist must claim sanctuary in "the purposes of discussion," and reasonable limits must be allowed to his refuge.

The cycle in human beings is customarily considered to be about 28 days long, with flow starting on each twenty-ninth day. The inaccuracy of this concept has already been shown (Fluhman[9] and Haman[10]). Our analysis of six consecutive cycles recorded by each of a sample group of 100 young fertile women, all wanting to know their ovulation time for contraceptive purposes, is confirmatory. Most normal cycles are within the range of 28 ± 4 days; that is, normal menstruation usually starts not earlier than the twenty-fifth day nor later than the thirty-third day of a given cycle. Excursions beyond these limits among our group of 100 normal women, however, were not infrequent. Twenty-one patients, during the recorded six cycles, jumped the range, once; 18, twice; and 12, three or more times. Of the six hundred cycles, there were ninety-nine (16.5 per cent) beyond the range of 24 to 32 days. I believe it is fair to consider that menstruation is, to some extent, disordered if it habitually occurs oftener than the twenty-fifth day or less frequently than the thirty-third day. As previously stated, the typical normal cycle may be considered as 28 ± 4 days.

Most women who ovulate regularly will be found during six consecutive months to menstruate within this wide range and often within narrower limits. If x be taken to mean any one figure within the span of 28 ± 2 days, then $x \pm 2$ days, which at most will be 28 ± 4 days, limits the range of 38 of our 100 sample patients. Eleven more had only one cycle greater or less than this; 13 had two; 2 had three; and the other 36 were moderately irregular, although they sometimes menstruated within the limits of 28 ± 4 days.

Amount and Quality of Bleeding

When the nonhormonal factors of clotting, tissue-repair, muscle tone and blood supply are normal, the amount and duration of bleeding and the quality of the discharge are roughly proportional to the degree of proliferation and to the area of tissue destruction. Of influence also is the length of time during which the bleeding potential is activated. Throughout the two weeks of luteal function, progesterone stimulates a fairly uniform development of the predecidua over most of the fundal cavity, and does it to the same extent during progressive cycles, so that the amount of tissue developed and the area covered are repeatedly essentially the same. Furthermore, when the bleeding potential in this tissue is activated on the withdrawal of estrogen and progesterone, the bleeding mechanism is started

over the whole area, usually within forty-eight hours. Promptly thereafter, recontraction of the arterioles, clotting and repair processes function, and in due time the bleeding ceases. Thus in cycle after cycle the amount and the duration of the flow are similar.

When ovulation fails, and there is no luteal hormone, estrogen from an indefinite and ever-changing number of well developed follicles establishes a bleeding potential of equally variable intensity in an endometrium that has proliferated in different degrees. According to the Smiths,[8] "Bleeding when it does occur due to temporary drops in estrogenic support to the endometrium, fails to be accompanied by 'the trigger' mechanism of both hormonal and endometrial origin that makes for normal follicle maturation and periodicity." Furthermore, activation in the solely proliferative endometrium, unlike that in the secretory tissue, is not fairly synchronous over the whole area, often occurring in patch after patch during many days or weeks. Thus in successive periods of flow are the amount and the duration of the bleeding and the quality of the discharge variable in the absence of ovulation.

Again for purposes of discussion, one must be somewhat arbitrary in defining the limits of the flow of normal menstruation. It varies in amount from day to day and in the number of days during which it persists. In general, it lasts for not more than seven days and not less than three, and requires an average of four napkins a day. A discharge that stops sooner or is less profuse than these limits, constitutes hypomenorrhea. Mild degrees of this seem to me to be more frequent than hypermenorrhea, which exceeds either of these limits.

Disorder in Frequency of Flow

The dominant qualities of flow may be listed as periodicity, frequency, duration and amount. Since the incidence, the length and the quantity of flow may vary from what may be considered typical of normal deciduation, there appear various forms of menstruation, not all of which should be considered harmful. One distinguishing characteristic of normality is almost always present. This is periodicity (measurability or regularity) of the recurrent cycles. Except in cases of extreme oligomenorrhea, whenever flow occurs aperiodically (immeasurably or irregularly) one may be sure that ovulation is incomplete or more infrequent than are the phases of flow. Aperiodomenorrhea then is abnormal; for it bespeaks a failure of ovulation. Reference to what has been written above concerning the role of the luteal secretion, progesterone, both in temporary inhibition of follicular development and in the metabolism of estrogen, will explain the relation: biopsy on the first days of irregularly recurring catamenia will prove it. As failure of ovulation is dysfunction, this type of flow, aperiodomenorrhea, is dysfunctional. Further consideration of it is postponed.

Among the forms of functional, therefore periodic, flow are oligomenorrhea (few periods) and polymenorrhea (many periods), as well as hypomenorrhea (little flow) and hypermenorrhea (much flow). All these forms, with the occasional exception of marked oligomenorrhea, have a discernible periodicity. This is because the fortnightly luteal function of the ruptured follicle is more or less unimpaired. But luteinization also ensures two other qualities of a flow that is functional — duration and amount. Reconsideration of the parts played by estrogen and progesterone in the formation and integration of the predecidua and the bleeding potential and of how deciduation occurs will show why this is so.

Amenorrhea

This is but a comparative term, as applied to otherwise normal menarchial women, for failure to flow, usually is limited to months or years: almost never is menstruation completely absent from puberty to the menopause. As against oligomenorrhea (few periods), what infrequency should be called amenorrhea? Customarily, it is that of four months or more, although flow may be absent for many years.

Except possibly in the very rarest of cases, mentioned above, in which there is absence only of the bleeding potential, — theoretically a sensitivity of the specialized arterioles to the catabolic products of the endometrium, — failure of menstruation reflects failure of ovulation. The hypophysis does not secrete proper amounts of follicle-stimulating or of luteinizing hormone, or the primary follicles, for some unknown reason, are insensitive to normal hormonal stimulation. When pituitary failure is not evidenced by dysfunction of the other endocrine glands, there is usually only partial lethargy of the follicles. In some cases it is surprising how nearly many of these approach normal size, giving estrogen titers of low normal values and thus stimulating a fair degree of endometrial proliferation; however, neither an egg matures, nor is the decrease in estrogen sufficient to cause destruction of the endometrium. Thus amenorrhea is essentially a gross dysfunction of ovulation.

Oligomenorrhea

When cycles are habitually longer than thirty-two days, the condition is termed oligomenorrhea (few periods). In 100 barren women, we found only 4 with this condition; among 100 fertile women, there were 7. If the phases of flow resemble each other in duration, quality and quantity of discharge, biopsy during the week before flow will almost certainly show that ovulation took place about fourteen days before the menses appeared. Women who menstruate at long intervals, but always similarly, ovulate at equally long intervals and thus function normally during approximately four weeks before

the onset of flow. Preceding these four weeks, there is disruption of the reciprocal activity of the pituitary gland and the ovary. When the interplay takes place, it performs in proper fashion. True oligomenorrhea is thus a disorder of ovulation rather than a dysfunction of menstruation.

Polymenorrhea

When a woman usually, not necessarily always, flows periodically (measurably or regularly) oftener than every twenty-fifth day, she may be said to have polymenorrhea. Of 100 reasonably fertile patients in our Rhythm Clinic, only 1 fell into this group; of 100 periodically menstruating barren women in our Fertility Clinic there were none.

Biopsy studies reveal several facts of great clinical significance among patients with polymenorrhea.

In the first place, there is a lower limit to the frequency of functional (postovulatory) flow at twenty-one days. Almost, perhaps all, women who flow consecutively as early as the twenty-first day following the onset of previous menstruation will be found to have only a proliferative endometrium, thus manifesting the nonovulatory or dysfunctional nature of the flow.

Secondly, probably more than half of those with polymenorrhea — that is, those whose cycle lengths lie between twenty-two and twenty-four days inclusive, — show in their endometrium, at the time of flow, a luteal influence of about fourteen days' duration. These therefore ovulate at the normal time in their cycles — about the fourteenth day of flow, although earlier than the fourteenth day of the cycle. The shortening of the cycle occurs in the preovulatory phase, when the follicles grow and an ovum matures. The postovulatory or luteal phase extends for about fourteen days, as is usual in patients of normal range.

Thirdly, some with such short cycles are discovered by biopsy to flow from an endometrium that shows less than a fourteen-day luteal influence: the endometrium at menstruation is secretory but not of the ripe predecidual type. These women then ovulate less than fourteen days before the onset of the succeeding flow, an important deviation for the purposes of contraception by periodic continence.

Finally, an occasional patient complains of menstruation as often as every two weeks, or that discharge reappears for a few days about a week after menstruation has ceased. Biopsy reveals that such patients flow alternately from a full secretory and from a late proliferative endometrium. Their real menstrual periods occur within usual time limits: the intermediate phases of flow occur about fourteen days before the period, at ovulation time, and are merely an exaggeration of the ovulatory bleeding that doubtless takes place in all other women to a less extent, at or just after ovulation. (Hartman[11] found this in 75 per cent of his monkeys.) It is usually so slight as to pass unnoticed, often consisting of only enough to give the cervical mucus a transitory dark-brown tinge. In case the flow is noticeable, only alternate periods resemble each other. The condition, furthermore, is usually but transitory and intermittent.

Disorder in Duration or Amount of Flow

Hypomenorrhea

Very occasionally the clinician sees a woman whose cyclic flow obtains for only a day or two, or one whose discharge requires only one or two napkins a day. The endometrium in these cases, although constituting a true predecidua, is usually not so thick as commonly found: the cytologic make-up, denoting the effect of estrogen and progesterone, is the same, but there is a paucity of tissue. It is possible that in some of these cases the qualities of the nonhormonal factors are reversed. Parenthetically, it may be said that this condition has not been found to cause infertility. The tiny trophoblast apparently finds, even on this thin mucosa, all that it needs for implantation, and its stimulating influence provides the necessary increase of tissue.

Hypermenorrhea

Prolonged or voluminous phases of flow, which resemble each other, whether at normal intervals or as in polymenorrhea or oligomenorrhea, will be found on biopsy to come from a true predecidual lining. In such cases, there is no cytologic evidence of deficient corpus-luteum secretion. Sometimes, just before the flow begins the endometrium is thicker than it is in most cases, but the constituents are the same.

Reference to the foregoing discussions of nonhormonal factors of flow makes it clear that retardation of clotting or of repair of the areas exposed by denudation, with their many torn capillaries or severed arterioles, as well as delay in the reconstriction of arterioles, may permit prolongation of hemorrhage although the hormones involved are in normal concentration and proportion. Similarly, a conceivable inordinate complexity of the vascular tree or an undue venous pressure may increase the number of bleeding vessels; or myometrial atonia may allow comparative hypertension in the terminal arterioles that are opened by disruption of tissue. But just as there is a disparity between bleeding potential and endometrial proliferation in some cases of dysfunctional flow from a hypotrophic mucosa, so, theoretically, in functional flow from a predecidua the hormones involved may set up exaggeration of bleeding while causing only the ordinary degree of tissue development. This hormonal disorder is believed to be mainly one of luteal secretions.[6]

Disorder in Frequency, Duration and Amount of Flow

Aperiodomenorrhea

By derivation, aperiodomenorrhea means immeasurability and therefore unpredictability of the onset and of the quality, quantity and duration of flow. Under this diagnosis fall the vast majority of menstrual complaints, only amenorrhea and hypermenorrhea approaching it in frequency, although the incidence of other deviations may be greater. Reconsideration of what has been written concerning the role of the corpus luteum in regulating the maturation of ova, and the oxidation of estrogen, will disclose that in aperiodomenorrhea the basic fault is in the formation of a luteal body. Since there is no clear evidence that, in human beings ova are not matured and released without subsequent formation of a corpus luteum, and vice versa, or that this gland ever forms without preliminary rupture of the ripe follicle, it may be assumed that in this condition there is failure of ovulation. Biopsy and surgical inspection substantiate this. Follicles grow and nearly ripen in varying numbers for variable periods, but none pass the rupture stage. I say "none"; but this is only a manner of speaking: the anovulatory woman may ovulate anytime. Hence, interspersed among months of ovulatory dysfunction there may occur an unrecognized normal cycle. Such cases are rare. Once a corpus luteum is formed, a succession of functional periods usually follows.

The affected patient is identified by the record of her phases of flow. Whenever in incidence they vary widely, sometimes by not much more than 28 ± 4 days, and, as is usually the case with such irregularity, they likewise vary in duration, quality and quantity of flow, this aperiodicity, this immeasurability, is sure to be associated with the presence of unruptured follicles and the absence of a corpus luteum. This is what the writers of a decade ago argued about as "anovulatory menstruation," and what before that was called "dysfunctional flow," "uterine dysfunction," "uterine insufficiency" or "metropathia haemorrhagica," and what frequently still is, I think, fuzzily dubbed "menometrorrhagia."

It is not infrequently interrupted by long or short sessions of amenorrhea; for the causal ovarian dysfunction common to both conditions varies within them only in degree of follicular development. Oligomenorrhea may resemble it, since here, too, the long cycles vary in length; but there is one clear distinction — in oligomenorrhea the phases of flow, when they come, are similar in duration, quality and quantity, whereas in aperiodomenorrhea, these vary in easily perceptible degree.

Treatment

The objectives of treatment for several of the disorders of menstruation are clear: the means, unfortunately, are not. As regular ovulation at intervals of about twenty-nine days, with subsequent flow requiring an average of about three napkins a day for about five days, is considered an acceptable "curse" by most women, such is the therapeutist's objective. As will be seen, the methods at hand for controlling ovulation, apart from suppressing it, are lamentably deficient. When, therefore, it occurs, even but rarely, as in oligomenorrhea, nothing but general hygienic measures and encouragement should be used. The same is true for most cases of true, functional polymenorrhea, which are fortunately not frequent. We have no means for retarding ovulation without endangering it. In the occasional case of polymenorrhea, when the shortening of the cycle is due to a premature decadence of the corpus luteum, daily increments of 0.1 or 0.2 mg. of diethylstilbestrol may be tried. This has been shown in the laboratory to stimulate the gonadotropic activity of the hypophysis,[12] and in the clinic, to delay menstruation, possibly by the same process. In larger doses, and indeed occasionally in those mentioned, it may have the undesired effect of estrogen in general — that of inhibiting ovulation.

Here it is pertinent to mention those cases of infertility with apparently normal menstruation in which biopsy shows that ovulation is delayed and yet flow occurs within the normal time, because the corpus-luteum phase is comparatively curtailed and catamenia takes place from an only partially developed predecidua. Davis and Hamblen[13] have designated these patients as those "bleeding from immature progestational endometrium." For such, treatment with small doses of diethylstilbestrol may also be helpful.

Wholesome neglect is proper in cases of noticeable ovulatory bleeding at the so-called "midperiod," a condition that is a kind of pseudopolymenorrhea. In suppressing it one may easily upset the hormonal balance on which normal ovulation depends. Patients with it are best reassured and let alone.

Because also to increase flow there is no dependable means that may not interfere with the ovulatory mechanism, no treatment but general medicine is indicated in hypomenorrhea. To be sure the emergence of this type of catamenia after years of more classic performance may occasionally presage the approaching climacteric. Even so, general supportive measures must suffice.

In hypermenorrhea, as in aperiodomenorrhea, the possibility of endometrial cancer must be ruled out by the prompt success of treatment or by curettage. Inspection of the cervix must be meticulous, and biopsy freely done.

When hypermenorrhea is of such a degree as to be very troublesome or to entail the loss with each catamenia of more blood than is easily replaced in the intervals between periods, something must be done. Attention should be directed first to the nonhormonal factors of bleeding: anemia must be relieved, the diet must be perfected, and pelvic congestion must be alleviated (often only knee-chest

exercises or a supporting pessary is necessary). If these measures fail, recourse may be had to the somewhat uncertain, and often not wholly satisfactory, hormones. Progesterone, in doses of 10 mg. on the second or third day of flow, sometimes suffices, although it may prolong the need for protection. Testosterone propionate is cheaper, and in doses of 10 mg. may likewise be effective. An intramuscular injection of 500 units of chorion-hormone on the second day of the period is also often beneficial. Unfortunately, this may cause malaise, pain in the neck and even moderate pyrexia, as if from a protein reaction. Prolactin has also been favorably mentioned,[14] but I have had no experience with it. I have not found extracts of ergot helpful, but others still recommend their use. Nor can I endorse the use of so-called "hemostatic doses of estrogen." They seriously endanger ovulation and are almost certain to be followed by withdrawal bleeding, both of which are undesirable sequelae.

In severe cases, recourse may be had to curettage, which the optimist will expect to be followed by several periods of acceptably diminished flow. It is not likely to give permanent relief. Since this condition is usually found in women over thirty-five, who wish, or can have, no more children, hysterectomy is not seldom the best cure.

In aperiodomenorrhea, anovulation is the basic cause. Ovular maturation, with consequent follicular rupture, is therefore the aim of treatment. I know of no dependable or even promising method of inducing this desirable effect. Nonetheless, therapeusis is not wholly futile: it is easy to relieve the patient's complaints of aperiodicity and unpredictability of flow, although it is seldom possible to rectify the fundamental follicular dysfunction. Time and hygiene are of appreciable assistance but should not be permitted to endow with specificity any particular method of treatment. All this can likewise be said of amenorrhea, the result of similar but more extensive ovarian deficiency. With one exception, then, the treatment of both conditions is the same.

Zondek[15] among others discovered the secret of occasionally establishing periodicity. Twenty-five milligrams of progesterone, given intramuscularly and, I believe, preferably divided into five daily doses of at least 5 mg. each, can be expected to stop anovulatory bleeding and to be followed within ten days, usually within four, by satisfactory flow. Rarely will more bleeding occur before twenty-eight days have passed. If on the twenty-ninth day another similar series of injections is given, again flow will follow at about the same interval. Properly this routine is repeated five times. After six months, treatment is suspended. Sometimes the extensive but immature follicular development that induced the estrogenic proliferation of the endometrium and the bleeding potential will be so retarded as to impair these processes so that flow becomes scanty as the repetitive treatment progresses. This more closely approaches the condition found in amenorrhea. As in the latter disorder, some estrogen is then appropriately added to the treatment. One to two milligrams of dissolved estrogen is added to each 5 mg. of progesterone; or, perhaps preferably, 0.05 mg. of ethinyl estradiol or about 0.3 mg. of diethylstilbestrol is given orally daily during the twenty-one days preceding each series of progesterone injections.

Thus is the hormonal treatment of amenorrhea and of aperiodomenorrhea essentially the same. In the former, estrogen is lacking and must necessarily be added to the progesterone, since estrogen only can induce proliferation of the endometrium and establish the bleeding potential. In the latter, it is not at first and may not ever be required, since the condition is inaugurated by too much estrogen and successive series of progesterone treatments may retard but may not sufficiently impede follicular growth and estrogen production.

As has been said, the above treatment will, at least for a time, bring about periodic flow in both amenorrhea and aperiodomenorrhea. But what is desired is ovulation that will do this and more without treatment. Fortunately, in about 3 per cent of cases, especially if minimal doses of or no estrogen is needed, spontaneous ovulation ensues. The Smiths[16, 17] postulate that this may be due to a "toxin" that they have found in the endometrium as it breaks down in the process so well observed in the monkey by Markee.[5] Is this the "menotoxin" named by Schick[18] in 1920 and only now approaching identification?

Other methods for inducing ovulation have received enthusiastic approval by various workers. I deplore the fact that I have not found them satisfactory. Small doses of x-rays have been proposed (Mazer and Israel[19] and Rock, Bartlett et al.[20]). This method sometimes increases the impediment to ovulation, and may possibly have a deleterious effect on the genes of all primitive ova. Gonadotropic extracts of mare's serum, as well as those from the pituitary glands of sheep, alone or preceding the injection of chorion-hormone, are apparently effective in other hands.[13, 21] The serum gonadotropins and pituitary extracts sometimes stimulate follicular growth and so evoke a modicum of bleeding in amenorrhea, but in the rare case in which ovulation has occurred, it seems to me to have been only coincidental. Chorion-hormone has happily outlived its fictitious value as a follicular stimulant. More potent extracts of animal anterior pituitary glands or the synthesis of the active follicle-stimulating and luteinizing hormones is hopefully awaited.

A word should be said of the use of thyroid as an ovarian stimulant. It is surely not a specific but may rarely help in cases with normal basal metabolic rates and more frequently in those whose rates are below normal.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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CASE 31521

PRESENTATION OF CASE

A forty-three-year-old carpenter entered the hospital complaining of vomiting.

Fifteen years before admission, during a life-insurance examination, albumin (400 mg. per 100 cc.), casts and a few red cells were found in the urine. At that time the blood pressure was 150 systolic, 100 diastolic. Five years before admission he noted the onset of nocturia, which became progressively worse. At about the same time he had episodes of epigastric pain after meals, which were relieved by food and soda. A duodenal ulcer was diagnosed and treated with Sippy powders and frequent feedings. The symptoms subsided, but the patient continued to have occasional attacks of epigastric discomfort. Ten months before admission he had an episode of pain in the right flank and costovertebral angle, followed by hematuria of one week's duration. Some time later he noted the onset of cramps in the legs and abdomen, restlessness and twitching of the eyelids. Eight weeks before admission he began to vomit, losing a large part of all food ingested. The vomitus occasionally resembled coffee grounds. Progressive dryness and scaliness of the skin appeared, with itching. He also complained of dyspnea, fatigue, anorexia, diarrhea (one to five watery stools daily), polydipsia and sleepiness during the day. Diminution of auditory and visual acuity, with photophobia, occurred. Frequency, nocturia and dysuria became worse. During this period he had lost 10 pounds.

On physical examination, the patient was pale and thin. The skin was dry, scaling and cold. The breath had a uremic odor. The eyelids were reddened, with fissuring of the lid margins. The pupils reacted to light and accommodation. Examination of the eyegrounds showed arterial narrowing and arteriovenous nicking. A "wooly" exudate and flame-shaped hemorrhages were present. The lips were cracked, and the oral mucous membranes pale. The left border of the heart was 9 cm. to the left of the midline in the fifth interspace. The cardiac rhythm was regular. The lungs were clear. The abdomen was slightly tense and tympanitic. The ankles showed pitting edema. Neurologic examination was negative.

The temperature was 97.4°F., the pulse 78, and the respirations were 24. The blood pressure was 185 systolic, 110 diastolic.

The red-cell count was 1,580,000, with 4.9 gm. of hemoglobin. The white-cell count was 9800, with 70 per cent neutrophils. The red cells showed marked anisocytosis and poikilocytosis and moderate achromia. The urine was yellow, cloudy and acid, with a specific gravity of 1.010. It gave a +++ test for albumin; there was no sugar, but the sediment contained many granular casts, 5 to 10 white cells and 100 red cells per high-power field. Many clumps of epithelial cells and white cells were present. The nonprotein nitrogen was 230 mg. per 100 cc., total protein 6.7 gm. per 100 cc., the sodium 144 milliequiv. per liter, and the chloride 95 milliequiv.

The patient became markedly dyspneic and orthopneic. Numerous bubbling rales were heard in

*On leave of absence.

the lungs. He was given morphine and laminophyllin, and an oxygen mask was used. He expired on the third hospital day.

Differential Diagnosis

Dr. J. Sidney Stillman: We have a man with a fifteen-year course of kidney disease who came to the hospital for the last three days of his illness, during which time certain observations were made. We can say that this man had Bright's disease, but to be more specific is not so easy. In my experience it is not only difficult clinically but sometimes pathologically to establish the exact sequence of events in the development of kidney disease.

In discussing this case it seems desirable first to attempt to determine the anatomic type of Bright's disease from which this patient died. Then, if time permits, we can take up the complications and the disturbances in body chemistry. I believe that the following diagnoses should be considered in the differential diagnosis: chronic glomerulonephritis, arteriolar nephrosclerosis, chronic pyelonephritis and polycystic disease of the kidneys.

There are no physical findings or x-ray evidence to support the last diagnosis. The presence of hypertension and the abnormal urinary findings fifteen years before death are also against it. Apparently there had been no bouts of infection and only one of gross hematuria, whereas one would expect more infection and hematuria in polycystic disease. This diagnosis must be considered, however, because it is known that patients suffering from it show evidence of renal failure between the ages of forty and fifty, and that the disease is slowly progressive. I doubt that he would have had hypertension so long before death, so I am in favor of discarding the diagnosis of polycystic disease of the kidneys.

The other three diagnoses are the likeliest possibilities. In the end stage, which was all that was observed in this hospital, they are difficult to differentiate. I am forced, however, to discard the diagnosis of chronic pyelonephritis because I can find no evidence in the history of an initiating attack of acute pyelonephritis or of recurrent attacks of headache, fever, backache and pyuria. Furthermore, the findings in the urine fifteen years before entry are not typical of this disease.

This brings us to a choice between chronic glomerulonephritis and arteriolar nephrosclerosis, and I find it a difficult one. When it was first discovered, fifteen years before death, that the patient had kidney disease, the urine showed albumin, red cells and casts, and there was also a slight hypertension. If we knew which abnormality had appeared first, our problem would be easier. The fact that these urinary findings were accompanied by only a slight degree of hypertension favors chronic glomerulonephritis. The duration of the disease from the time of discovery to death in a man of his age also points to chronic glomerulonephritis, which frequently has a long latent period. Gross hematuria, which he had on one occasion, occurs in nephrosclerosis but is more frequently found in glomerulonephritis. In comparing the degree of hypertension attained in the terminal phase in large series of cases of each disease one finds a higher average level in nephrosclerosis. In either group, however, it varies greatly in individual cases. It should also be pointed out that it is somewhat unusual for the blood pressure to rise so early in glomerulonephritis as it did in this patient. Another thing that makes me tend toward the diagnosis of glomerulonephritis is again a statistical one, namely, that only 10 per cent of patients with nephrosclerosis die from renal insufficiency, the rest dying of heart failure, vascular accidents or intercurrent infection. In this patient there was evidence of only slight to moderate cardiac hypertrophy, the left border of the heart being only 9 cm. from the midline, and I believe that in nephrosclerosis of this severity one is likelier to observe greater cardiac enlargement. For these reasons I favor chronic glomerulonephritis as being the initial kidney disease from which this man suffered. With his degree of hypertension one would expect arteriolar changes to have developed in the terminal phase.

During the last eight weeks of life, the patient developed uremia, which probably accounts for the appearance of dysuria, diarrhea, vomiting, anorexia, fatigue and sleepiness. I believe that the muscular irritability was due to a low blood calcium, which is the indirect result of the inability of the kidney to eliminate phosphates. As a result of the low blood calcium the parathyroid glands are stimulated, resulting in hyperplasia of these glands and some decalcification of the bones.

I have disregarded the history of ulcer, which might have accounted for the vomiting and in turn for the high level of the blood nonprotein nitrogen and also a value for the total protein that is higher than what I should have expected in a patient with this amount of kidney disease.

In conclusion, then, I favor the diagnoses of chronic glomerulonephritis, with renal insufficiency and uremia, hypertensive heart disease, with slight to moderate cardiac hypertrophy, and questionable hyperplasia of the parathyroid glands with accompanying osteitis fibrosa.

Dr. Chester M. Jones: This man represents one of the cases that never should have had alkaline therapy. If he had had it for a year continuously, the renal situation might have been aggravated, and that, accompanied by a milk diet, might have produced renal calculi.

Clinical Diagnoses

Chronic glomerulonephritis.
Pulmonary edema.

Dr. Stillman's Diagnoses

Chronic glomerulonephritis.
Hypertensive heart disease.
Parathyroid hyperplasia, secondary?

Anatomical Diagnoses

Subacute and chronic glomerulonephritis developing in congenital polycystic kidneys.

Bronchopneumonia.
Parathyroid hyperplasia, secondary.
Duodenal ulcer, healed.

Pathological Discussion

Dr. Ronald C. Sniffen: As expected, the primary disease was found in the kidneys. The left was enlarged to 200 gm., whereas the right was slightly below the average normal weight of 150 gm. Their surfaces were granular and somewhat pale, and the entire parenchyma, both medulla and cortex, contained thin-walled cysts, which varied in size from that of a pinhead to over 1.0 cm. in diameter and were filled with yellowish watery fluid (Fig. 1). In

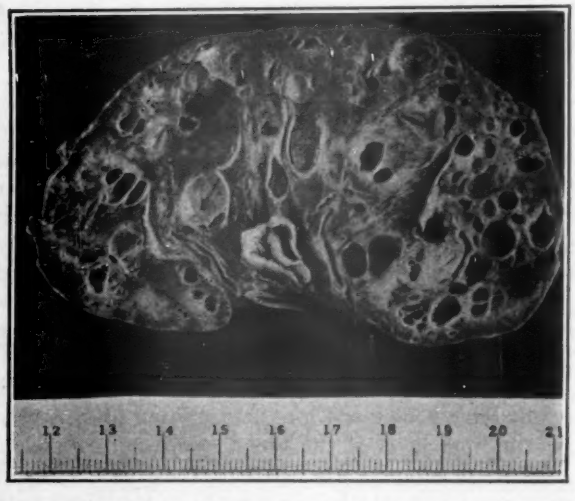

Figure 1. *Photograph of Left Kidney.*

brief, they were typical polycystic kidneys, but there seemed to be an unusual amount of unaffected parenchyma for this man to have died in uremia. Sections showed microscopically the usual picture of polycystic kidneys. The remaining parenchyma, however, revealed the unmistakable changes of subacute and chronic glomerulonephritis (Fig. 2). There was pronounced vascular damage, and some of the glomerular tufts were acutely inflamed.

In addition there was a bronchopneumonia as well as evidence of a healed duodenal ulcer. The parathyroid glands were slightly hyperplastic, but bone changes had not yet appeared. The heart was only slightly, if at all, hypertrophied, weighing 370 gm.

CASE 31522

Presentation of Case

A sixty-two-year-old man was admitted to the Emergency Ward complaining of abdominal pain.

Five days before admission he noticed cramping, generalized abdominal pain, which persisted and became somewhat severer. He lost his appetite and became nauseated, but there was no vomiting, jaundice or melena. There had been no recent weight loss.

Eight months before admission he had had an episode of cramping pain low in the abdomen, which subsided in five days. Two years before admission bright-red blood was seen in the stools on

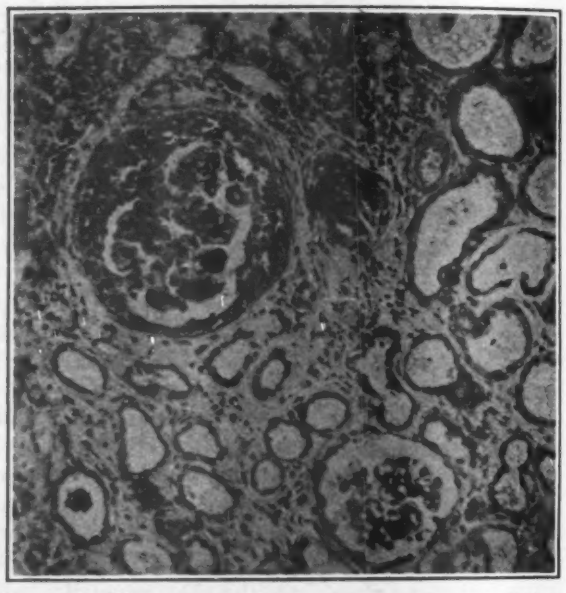

Figure 2. *Photomicrograph of a Section of the Left Kidney. Note the glomerular changes characteristic of glomerulonephritis.*

one occasion; following this, constipation developed and increased. The stools had never been tarry. Bitter gaseous eructations were noted, with occasional vomiting. There had been no hematuria.

Physical examination revealed a systolic murmur heard at the base of the heart. The lungs were normal. The abdomen was moderately distended, with generalized tenderness, particularly over a mass to the right of the umbilicus. This mass measured about 10 by 5 cm., and was dull to percussion; the mass was not fixed but did not move on respiration. It did not seem to be connected with the kidney or liver. Peristalsis was active. Rectal examination was negative.

The temperature was 102°F., the pulse 110, and the respirations 30.

Examination of the blood revealed a white-cell count of 25,200. The urine was normal. Stomach contents and a stool were guaiac negative.

After two days in the Emergency Ward, the white-cell count rose to 33,100 and the patient was admitted to the hospital. The abdominal pain was

subsiding. He had had two watery brown stools a day. The temperature was 99°F., and the blood pressure 120 systolic, 74 diastolic. The heart was not enlarged. A systolic murmur was heard over the base of the heart, transmitted to the apex and axilla. The pulse was strong and regular, at a rate of 88. The left shoulder was low, and expansion of the left chest was markedly decreased. The left half of the diaphragm was 2 to 3 cm. higher than the right half. An expiratory friction rub was heard all over the left chest, most marked at the base. There were a few fine rales in both bases. The abdominal mass was still present but less tender than before. Abdominal distention persisted, with normal peristalsis. There was no costovertebral angle tenderness.

During his stay in the hospital the white-cell count decreased steadily. The red-cell count was 4,500,000. On the third hospital day the nonprotein nitrogen was 32 mg. per 100 cc., the total protein 5.6 gm., and the chloride 94 milliequiv. per liter. The serum amylase was 39 units per 100 cc. (normal 15 to 35 units).

A flat film of the abdomen showed the colon to be filled with gas and fecal material over to the splenic flexure. Distal to this the bowel was outlined with gas without evidence of retained fecal material. No soft-tissue mass was recognized. The bones and joints of the lumbar spine and pelvis were not remarkable. A barium enema filled a loop of sigmoid that rose high out of the pelvis into the left upper quadrant. There was no rigidity of the wall. The remainder of the colon filled without evidence of disease. The mucosal pattern after evacuation was not remarkable. The appendix filled, but the terminal ileum did not. A small area of calcification lay to the right of the first lumbar interspace 4.5 cm. from the spine. A gastrointestinal series was negative. An intravenous pyelogram revealed normal kidney outlines. The psoas muscles were symmetrical. The liver and spleen were not enlarged. The intravenous dye was excreted promptly and in good concentration, outlining nondilated upper urinary passages. The bladder shadow was not remarkable. There was another indefinite area of calcification medial to that previously described. It could not be localized. On a chest plate, the lung fields were clear, as were the costophrenic sinuses. The diaphragm was limited in motion. The heart was within normal limits. The aorta was markedly tortuous. A Graham test showed a gall bladder filled with well concentrated dye. Following a fatty meal the gall bladder was seen to contract.

An operation was performed on the seventh hospital day.

Differential Diagnosis

Dr. Oliver B. Cope: I should like to ask when the serum amylase test was done.

Dr. Benjamin Castleman: It was done four days after admission.

Dr. Cope: The amylase test used in this hospital is based on the amount of reducing sugar produced from starch after fifteen minutes of incubation of the patient's blood serum with starch. The normal values range between 15 and 35 units. This reading of 39 is therefore just above the limit of normal.

After reading this record I can entertain but one diagnosis and that is acute pancreatitis. Let me tell you why I make that diagnosis. The history is not too characteristic or too helpful. It fits with many conditions, but I take some comfort from the apparent difficulty that the service had in making a diagnosis in the first days.

On physical examination there were a tender abdominal mass and intestinal distention. There was initially nothing to indicate that this mass was retroperitoneal beyond the fact that it did not move with respiration. One could properly consider several retroperitoneal masses, such as aortic aneurysm, for instance; but these I shall pass over. The mass might have been an acutely inflamed, low-lying gall bladder, not intimately bound to the liver. In two days, however, there were signs that the left side of the diaphragm was elevated, and the mass is recorded as less tender. It would be hard to tie together decreasing inflammation of a right-sided gall bladder and the simultaneous development of a high diaphragm on the left. But such a dual involvement of right and left sides is characteristic of acute pancreatitis, for with the spread of inflammation out from the body and tail of the pancreas into the lesser peritoneal cavity, elevation and fixation of the left half of the diaphragm is the rule, even though no mass may be felt on the left side of the abdomen. The right subdiaphragmatic space is not similarly involved because the liver blocks the way. That the mass and origin of the elevation of the left diaphragm did not lie in the urinary tract is suggested by the absence of costovertebral tenderness and the unlikelihood of spread of inflammation from the right kidney to the left subdiaphragmatic space.

That acute pancreatitis became apparent as a possible diagnosis is indicated since on the fourth hospital day a serum amylase test was made. The x-ray examination offers comforting confirmation of this point of view. The right kidney and the intestinal tract are excluded as sources of the mass. There is partial obstruction of the colon at the splenic flexure, and at first sight there would seem to be disease of the colon. One cannot, however, put together obstruction of the splenic flexure, a right-sided mass and primary disease of the colon. But this triad is just what acute inflammatory disease of the pancreas can do. A considerable mass can be produced by inflammation in the pancreas and retroperitoneal area, and it can, and indeed occasionally does, simulate large-bowel intestinal

obstruction. Not long ago we had a patient with obstruction at the hepatic flexure with a positive diagnosis by x-ray of carcinoma of the hepatic flexure that turned out to be pancreatitis. A mass arising in the head of the pancreas on the right side had projected laterally, compressing the right colon. The findings in the colon here could be explained by a massive pancreas, the body and tail of the pancreas involving the splenic flexure. It could also account for the high diaphragm on the left, because there may be a considerable amount of fluid in the lesser peritoneal cavity. Indeed, there may be diaphragmatic pleurisy and fluid in the chest. I suspect that the surgeon went in to drain a large accumulation of fluid. These accumulations can rapidly occur.

A patient with acute pancreatitis can have a normal Graham test, but it is not usual. The incidence of pancreatitis is much higher in the presence of gall-bladder disease. The acute, hemorrhagic, fulminating type of pancreatitis is the one that exists more frequently in the absence of gall-bladder disease. In this patient we are dealing with something much less fulminating. The patient survived five days before entry and seven days in the hospital before operation, which he presumably survived. It is therefore a less fulminating type of disease and is likelier to have been associated with gallstones. Furthermore, a negative Graham test does not exclude small gallstones.

An abdominal tap would have furnished valuable information. In cases suspected of having acute pancreatitis a tap should be carried out in the left gutter of the peritoneal cavity. If consommé-like fluid is withdrawn the diagnosis is virtually established, because with enzymic irritation and fat necrosis involving the peritoneal surface there is usually, in fact one might say always, an excessive amount of fluid, which has a characteristic gross appearance. Not only is the color like that of consommé but there may be fat deposits floating on the surface. I should like to emphasize the clinical usefulness of this single test. It can be carried out safely in the early hours of the disease before there is danger of adhesion of the intestinal wall to the parietal peritoneum. The serum amylase test in acute pancreatitis is also diagnostic. In this case it was done nine days after the onset of the disease, and although it is a borderline value, it does not exclude the diagnosis in this patient. The characteristic curve of the amylase test in both the blood serum and the urine is that it rapidly reaches a peak after the onset of the disease and slowly subsides; it may be normal at the end of seven days, so that one cannot be absolute about the diagnosis thereafter. Acute pancreatitis certainly seems to be the most logical diagnosis, and although I suspect that Dr. Castleman has some trick up his sleeve to catch me, I cannot make any other diagnosis.

Dr. Francis D. Moore: I should like to point out that an elevated amylase is not diagnostic. It can be produced by a host of other conditions in the abdomen. If it is elevated above a certain level, yes; but when it is borderline like this, I do not believe that it should be considered diagnostic.

Dr. Copp: I agree. There is only one disease that I know of that gives a really high serum amylase level, namely, obstructive occlusion of the pancreatic duct and its consequences. Acute pancreatitis apparently gives a comparable picture. The amylase activity rises with the same sequence if the pancreatic duct is ligated at operation — a high abrupt rise, with gradual fall and return to normal. Such a rise occurs following ligation of any portion of the duct, as for example following extirpation of the duodenum. The explanation suggested by Elman* of St. Louis is, I believe, the correct one. This amylase, an enzyme, is intended for the intestinal tract. It is the external secretion of the pancreas. When backed up by ductal ligation associated with inflammation in the pancreatic tissue, the enzyme is absorbed into the blood stream. As the inflammation subsides there is no further excess. It is believed not to be the amylase enzyme that normally exists in the blood stream.

Clinical Diagnosis

Acute pancreatitis.

Dr. Cope's Diagnosis

Acute pancreatitis.

Anatomical Diagnosis

Acute pancreatitis, with fat necrosis.

Pathological Discussion

Dr. Rodolfo E. Herrera: The operation was a peritoneoscopy. We saw a mass to the right of the umbilicus. This mass was behind the omentum and gave the impression of being retroperitoneal. The entire peritoneum, anterior gastric wall, small bowel and liver were covered with small pale, yellowish implants averaging 2 mm. in diameter. Never having seen fat necrosis through a peritoneoscope I did not know whether they were fat necroses or carcinomatous implants. Nor had Dr. Benedict seen fat necrosis through the peritoneoscope, so we did not know which of the two it was. At the time of peritoneoscopy no free fluid could be seen in the abdominal cavity; that does not mean that there was none previously. We removed one of these small implants.

Dr. Castleman: The biopsy did show fat necrosis, so that there is no doubt that the disease process was acute pancreatitis. The patient went home two weeks after peritoneoscopy. Have you seen him since?

*Elman, R. Variations of blood amylase during acute transient disease of pancreas. *Ann. Surg.* **105**:379-384, 1937.

DR. HERRERA: No. By the time he went home the mass had decreased markedly in size. The abdomen was no longer tender, and the temperature was within normal limits.

* * *

Addendum. The patient was seen in the Out Patient Department three weeks after discharge. He was asymptomatic, and abdominal examination was negative. No mass could be felt. He returned to the Emergency Ward, however, three weeks later, just two months after the peritoneoscopy, with the story that three days before he was seized with a sudden severe pain in the right upper quadrant that radiated across the epigastrium to the left upper quadrant. This pain was associated with nausea and vomiting. He was readmitted to the hospital.

Physical examination showed tenderness in the right upper quadrant. The serum amylase was only 11 units per 100 cc. After a Graham meal the gall bladder was not visualized, and it was decided to remove the gall bladder and to explore the common duct. At operation, fat necroses, some of them already calcified, were scattered over the pancreas and omentum. There was no evidence of an acute process. The gall bladder was removed. No stones were found in either the gall bladder or the common duct. The patient left the hospital two weeks later and was free from symptoms.

An index of the diagnoses and discussers of the Case Records for the year 1945 will be found elsewhere in this issue of the *Journal*.

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Journal of Medicine

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MCMXLVI

The value of a New Year is that it brings with it, or seems to bring with it, an opportunity to wipe the slate clean of the mistakes of the dying year, and to make a fresh start. Of course we can make a fresh start at any season of the calendar, but it seems more fitting to do so at its close. New Year's Eve means curtains, and the next day starts a new act and, we always hope, a happier one.

It is a good thing to have this symbolic "fresh start" as a sign of a certain flexibility of mind — an earnest of our desire to be better and to do better in life than the frailty of our mortal cosmos had hitherto permitted. It means that, weak as we are, we want to be good — at least those of us who make our New Year's resolutions with any degree of seriousness.

We must frequently give way to the sad reflection that not many of our happy new years of the past have remained happy for long, owing both to our own failings and to the folly of others. Life, which may be gracious, effective and productive, is filled with inner tensions and with anxieties over the curse of mankind — the drive for getting and spending or getting and keeping. The curse of acquisitiveness, of getting the better of someone else and of having more than our neighbor has, whether as an individual or as a nation, has blighted much of the happiness that might otherwise have existed in the world.

Wordsworth, in an earlier period of world unrest, felt much the same emotion when he wrote his sonnet to the world.

The world is too much with us; late and soon,
Getting and spending, we lay waste our powers:
Little we see in Nature that is ours;
We have given our hearts away, a sordid boon!

It is not intended to imply that there is not and cannot be happiness in life, despite the destructive influences of unfavorable environmental factors. Any life can be happy if it will give to material values only their due and retain sufficient intellectual and emotional flexibility to face what the year will bring.

With this comforting thought and a firm belief in the desirability of new and better resolutions, we again find courage to wish our readers, sincerely, a Happy New Year!

ABUSE OF PENICILLIN

Last May when the War Production Board removed the restrictions on the distribution of penicillin, there was every reason to anticipate that its use would become widespread. When the manufacturers found it possible to reduce the price to a reasonable figure, the temptation to use it even more extensively and in larger amounts became greater. In the case of the sulfonamide drugs, at least some physicians exercised reasonable caution in prescribing them because of the toxic effects that so frequently accompanied their use. The rela-

tive freedom of penicillin from toxic side effects does not impose this limitation.

It is probably fair to say that penicillin is now being used in large amounts and in many conditions irrespective of any demonstrated beneficial effects. Until recently the only reasonable restraint that many physicians felt was caused by the necessity of giving the penicillin by injection. Thus, penicillin had to be administered either by a doctor or by a trained nurse and its use was essentially limited to hospitals or to homes in which private nursing service was available. In recent months, shortage of nurses and of hospital beds has considerably limited the ability of many physicians to prescribe the agent. Furthermore, the objections of patients themselves to repeated and prolonged injections have often reminded the physician that continuation of treatment could only be justified by reasonable indications.

It is in the hospitals, especially the larger ones, that penicillin has been most flagrantly abused, particularly from the point of view of the quantities dispensed. Orders for penicillin have been written lavishly for all patients with fever and for most of those in whom fever or infection might be anticipated, irrespective of any possible benefits that could reasonably be expected from its use. Interns and visiting physicians alike have shared in this spree. In one large Boston hospital alone, the amount of penicillin used in the past six months was equal to the entire world production only two years ago. The amount used in a single day in October was considered quite adequate, during the period when penicillin was being rationed, to fulfill reasonably the entire needs of all the patients of the same hospital over a period of three months. In another large Boston hospital, one of its administrators made a brief survey of the use of penicillin when the amount of money expended for this drug was found to be equal to the total amount being spent for all other drugs. It was obvious that totally excessive amounts were being given, that patients were receiving injections without any reasonable indication and that the drug was being continued almost indefinitely after the time when further benefit could be reasonably expected. Following this survey and certain recommendations, the amount used in the hospital declined from 60 to 80 per cent without interfering with the proper treatment of any patient.

It is not unlikely that the patients in the latter hospital actually benefited through this reduction in the amount of penicillin dispensed. Nursing services had been much curtailed, and the amount of nursing time that was released from unnecessary penicillin injections was undoubtedly well used for the essential care of patients. Furthermore, when penicillin is not given until there is reasonable evidence that it is indicated, or if it is discontinued promptly after a brief but adequate period has demonstrated that it is not producing a desirable result, the patient will benefit because then the physician will make a greater effort to arrive at a proper diagnosis and a more reasonable method of therapy.

At present, when the incidence of infections requiring penicillin therapy is greatest, there is an acute shortage of penicillin. This is due to many factors not easily controlled. It would be well for physicians to take stock of their use of penicillin from time to time and to be sure that they are prescribing it in a reasonable manner. The fact that large doses may be safely given does not mean that all patients should receive these amounts, which should be reserved for conditions in which big doses are clearly indicated. Furthermore, in cases in which prolonged treatment is not necessary, the drug should be discontinued at the earliest possible

MASSACHUSETTS MEDICAL SOCIETY POSTWAR LOAN FUND

The Postwar Loan Fund has been set up, and all discharged medical officers who were members of the Massachusetts Medical Society in good standing at the time of their entry into the service may apply for loans from this fund. For further information apply to:

George L. Schadt, *Chairman*
Postwar Loan Fund
8 Fenway
Boston 15, Massachusetts

moment. The widespread prophylactic use of penicillin in the treatment of colds or of uninfected wounds should be discouraged — particularly during the present shortage.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

LAWLER — William P. Lawler, M.D., of Lowell, died December 8. He was in his eighty-sixth year.

Dr. Lawler received his degree from the College of Physicians and Surgeons, Baltimore, in 1886. He was appointed to the staff of St. John's Hospital in 1891, served as city physician for three years and was a member of the Lowell Board of Health from 1891 to 1894 and again from 1932 to 1935. He was appointed to represent Lowell at the Pan-American Medical Congress in 1893. He was dean of physicians in Lowell, having been a practitioner since 1888. He was president of the Middlesex North District Medical Society in 1917. Dr. Lawler had been in semiretirement for several years.

His widow, three daughters, a son and a sister survive.

MISCELLANY

DEACONESS HOSPITAL TO CELEBRATE FIFTIETH ANNIVERSARY

In commemoration of the fiftieth anniversary of New England Deaconess Hospital, a dinner will be held on Wednesday evening, January 30 at the Parker House, according to a recent announcement by Dr. Warren F. Cook, Administrator.

Speakers will include Dr. Elliott P. Joslin, medical administrator of the George F. Baker Diabetic Clinic, Dr. Frank H. Lahey, surgeon-in-chief of the hospital, Mr. Everett Jones, vice-president of *Hospital Management*, Dr. Nathaniel P. Faxon, president of the Boston Hospital Council and director of the Massachusetts General Hospital, and Mr. Howard Brewer, president of the Board of Trustees of the hospital, who will preside. Head-table guests will include Dr. Carl S. Ell, vice-president of the Board of Trustees of the hospital, Stanley MacMullen, chairman of the Executive Committee, Mr. and Mrs. Ernest Howes, Mrs. Alexander Grant, Mr. and Mrs. William Snow, Jr., Dr. Charles Wilinsky, director of the Beth Israel Hospital, and other prominent civic leaders of Boston.

A financial drive is now in process at New England Deaconess Hospital to obtain funds for the addition of 200 beds, which will enable the hospital to serve more than 10,000 patients annually.

DIRECTORY OF APPROVED SURGICAL TRAINING PLANS

Chiefly as an aid to medical officers returning from war duty, the American College of Surgeons has published a 424-page directory in which are listed and described the approved programs of graduate training in surgery in two hundred and forty civilian hospitals in the United States and Canada, and in thirty-two Navy, seven Veterans Administration and ten United States Public Health Service hospitals. The total number of approved training plans comprise two hundred and twenty-eight in general surgery and five hundred and twenty-two in the surgical specialties — fractures, plastic surgery, proctology, thoracic surgery, neurologic surgery, orthopedic surgery, urology, obstetrics and gynecology (combined and separately) and ophthalmology and otolaryngology (combined and separately). In these seven hundred and fifty training plans, approximately two thousand surgeons may be trained, whereas, as the College points out, training facilities for at least five thousand are urgently needed for returning medical veterans whose training in surgery was interrupted by their military service. Publication of the directory is expected to stimulate the formation of additional programs of training in suitable hospitals.

The descriptions of the approved programs include information about the size and type of hospital, organization of the medical staff, facilities for study of the basic medical sciences in their application to surgery, library facilities, clinical material, manner of selecting individuals for training in surgery, scope and method of surgical training, supervision by the medical staff, examination and thesis requirements and provision, if any, for conferring higher medical degrees.

NOTICES

Dr. Leo Alexander, having returned from military service in the United States Army, announces the opening of his office at 433 Marlborough Street, Boston, for the practice of neurology and psychiatry.

Dr. Edward Blank announces the removal of his office for the practice of psychiatry and neurology from 205 Ellis Building to 1102 West Culver, Phoenix, Arizona.

Dr. Jacob Brem, returning from military service, announces the reopening of his office at 796 Pleasant Street, Worcester, for practice limited to the care of children.

Dr. Allan L. Davis, having returned from military service, is resuming the practice of surgery at 520 Commonwealth Avenue, Boston.

Dr. Rose C. Munro announces that, by error, her name was omitted from the new *Telephone Directory*. Her office address is Hotel Braemore, 466 Commonwealth Avenue, Boston (KEN 4600) and her residence address, 128 Marlborough Street, Boston (COM 0193).

Dr. Joseph A. Sapienza, having returned from military service, announces the opening of his office at 12 East Haverhill Street, Lawrence, for the general practice of medicine and surgery.

Dr. Herbert Sherwin, having returned from military service, has resumed the practice of pediatrics at 371 Commonwealth Avenue, Boston.

Dr. Claude E. Welch, having returned from military service, is resuming the practice of surgery at 266 Beacon Street, Boston.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 3, at 7:15 p.m. in the classroom of the Nurses' Residence. Dr. Gulli Lindh Muller will speak on the subject "Clinical Significance and Diagnosis of Jaundice."

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, January 8, at 8:15 p.m. There will be a symposium on deep-vein thrombosis and pulmonary embolism. Dr. John Homans will preside.

PROGRAM

Leg Venograms during Operations. Dr. David Davis.
Femoral-Vein Ligations. Dr. Jacob Fine.
Preliminary Report: The treatment of a controlled group of patients with dicumarol. Dr. Gordon Donaldson.
Vena-Cava and Femoral-Vein Interruptions. Dr. Robert R. Linton.
Immediate and Late Results of Deep-Vein Thrombosis. Dr. John B. Sears.

(*Notices continued on page xvii*)

TICES (*Continued from page 832*)

EPH H. PRATT
AGNOSTIC HOSPITAL
Bennet Street, Boston
Lecture Hall, 9–10 a.m.
MEDICAL CONFERENCE PROGRAM

day, January 4 — The Management of the Psychiatric Patient by the General Physician. Dr. Mandel E. Cohen.

nesday, January 9 — The Etiology of Pruritus Ani. Dr. E. T. Whitney.

day, January 11 — Staphylocoagulase and Related Substances. Dr. Burnham Walker.

nesday, January 16 — Urologic Problems in the Army. Dr. Wyland T. Leadbetter.

day, January 18 — War and Nerves. Major Merrill Moore, U. S. A.

nesday, January 23 — Surgical Aspects of Gastric and Duodenal Ulcer. Dr. Edward A. Cooney.

day, January 25 — Some Aspects of the Mechanism of Heart Failure. Dr. E. M. Landis.

nesday, January 30 — Cholecystitis: Its diagnosis and treatment. Dr. Fernando Biguria.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. All morning conferences are open to the medical profession.

CIETY MEETINGS AND CONFERENCES

LENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING URSDAY, JANUARY 3

SDAY, JANUARY 3
7:15 p.m. Monthly clinical conference and meeting of the staff. New England Hospital for Women and Children.

DAY, JANUARY 4
*9:00–10.00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.
*10:00 a. m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.
10:50 a.m. Endocrinology and Dermatology. Dr. R. H. Williams. (Post-graduate clinic in dermatology and syphilology.) Amphitheater, Dowling Building. Boston City Hospital.

IDAY, JANUARY 7
*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

UDAY, JANUARY 8
*9:00–10.00 a.m. Medical clinic. Infants' Hospital.
*12:15–1:15 p. m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
8:00 p.m. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital.
8:15 p.m. Greater Boston Medical Society. Auditorium, Beth Israel Hospital.

DNESDAY, JANUARY 9
*12:00 m. Clinicopathological conference. Children's Hospital.
*7:15 p.m. Graduate seminar in pediatrics. Children's Medical Service, Amphitheater 3A, Massachusetts General Hospital.

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en to the medical profession.

ANUARY 3. New England Hospital for Women and Children. Page

ANUARY 4–30. Joseph H. Pratt Diagnostic Hospital. Medical conference program. Notice above.

ANUARY 7–APRIL 22, 1946. Metropolitan State Hospital. Eleventh graduate seminar in neurology and psychiatry. Page 314, issue of ptember 6.

ANUARY 8. Greater Boston Medical Society. Page 832.

ANUARY 9. New England Oto-Laryngological Society. Page 798, issue December 20.

ANUARY 10. Fatigue, Its Significance and Treatment. Dr. Frank N. an. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

EBRUARY 2. American Board of Obstetrics and Gynecology. Page 4, issue of October 25.

EBRUARY 4–MARCH 29. Health Education Institute. Page 746, issue December 13.

AY 13–17. American College of Physicians. Page 798, issue of De- ber 20.

STRICT MEDICAL SOCIETY

ORCESTER

JANUARY 9. St. Vincent Hospital.
FEBRUARY 13. Worcester State Hospital.
MARCH 13. Worcester Memorial Hospital.
APRIL 10. Hahnemann Hospital.
MAY 8. Annual meeting.

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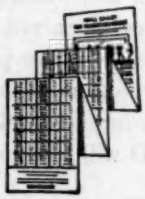

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